Intramolecular Conjugate Addition Nitro-Mannich Reaction

Towards the Synthesis of Schizozygine

A Thesis Presented by

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In Part Fulfillment of the Requirement for
the Degree of Doctor of Philosophy

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I, Christopher Denis Rundell confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Abstract

Part 1

The introduction of this thesis describes in detail the development of the nitro-Mannich reaction, in particular organocatalytic methodologies and its use in the synthesis of *N*-heterocycles. Additionally a current review of cascade cyclisations to furnish tetrahydroquinolines is detailed.

The results and discussion describes the strategies involved in synthesising sensitive nitrostyrenes tethered onto an imine. It was found that classical disconnections to nitrostyrenes, involving the Henry reaction, were successful but low yielding and with poor substrate scope. An alternative disconnection involving a condensation between 2-vinylanilines and aldehydes, then subsequent nitration with $AgNO_2$/TEMPO provided the desired nitrostyrene. It was found that this reaction sequence gave various substituted nitrostyrenes in high yields and was scalable.

The cascade cyclisation was then investigated using hydride and carbon nucleophiles. This was highly selective for either the *cis* or *cis*,*cis* diastereomer. Use of a simple thiourea catalyst and a Hantzsch ester as the hydride source gave access to these *cis*-tetrahydroquinolines in high enantioselectivities (up to >99% *ee*). Investigation into using chiral phosphine ligands for the enantioselective addition of carbon nucleophiles, such as dialkylzincs, failed to give any stereoselectivity. Briefly an enantioselective approach to *cis*,*cis*-tetrahydroquinolines is discussed, using a standard intramolecular nitro-Mannich reaction.

Part 2

The introduction to this section describes the Schizogane family of alkaloids, the approaches to their total synthesis and a review of both the nitro-Mannich reaction and the nitro group in total synthesis.

The results and discussion then details our approach to Schizozygine, the major alkaloid in the Schizogane family. Our retrosynthesis utilizes an intramolecular Pd catalyzed C-N bond formation and the enantioselective

synthesis of *syn*,*anti*-nitroamines, both methodologies have been developed within our group. The main body of this work describes the approaches for an enantioselective synthesis of the *syn*,*anti*-nitroamine and its use in the synthesis of a key piperidine intermediate.

Acknowledgements

I'd like to thank Prof. Jim Anderson for giving me the opportunity to work under him and for all his support and guidance. He allowed me to follow my own ideas and continued to give encouragement and support.

Thank you to the Anderson group, particularly Emily, Farzarneh, Helen and Steve for help with chemistry, enjoyable times in the lab and the pub, this also extents to James Rudman, our honorary Anderson group member.

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A special mention to Mr. Tilney, he kept me well enough to actually do my PhD and for that I'll always be grateful.

Thank you to my family, particularly my Mum and Brother; your care and support, whether it has been during my PhD or anytime during my life is greatly appreciated.

Abbreviations

Å	angstrom(s)
acac	acetylacetonate
AIBN	Azobis(isobutyronitrile)
Anal.	analytical
app.	apparent
aq.	aqueous
Ar	aryl
bipy	2,2'-bipyridine
Boc	*tert*-butyloxycarbonyl
BOP	(Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate
Bn	benzyl
BOX	bisoxazoline
br	broad
Bu	butyl
Calcd.	calculated
CAN	ceric ammonium nitrate
CI	chemical ionisation
COSY	correlation spectroscopy
Cy	cyclohexyl
δ	chemical shift
d	doublet
DBU	1,8-diazabicycloundec-7-ene
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DCE	dichloroethane
DCM	dichloromethane
DEPT	distortionless enhancement by polarization transfer
DIBAL	diisobutylaluminium hydride
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DMS	dimethylsulfide

de	diastereomeric excess
dr	diastereomeric ratio
E	electrophile
ECD	electronic circular dichroism
EDC	*N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide
ee	enantiomeric excess
EI	electron ionisation
equiv.	equivalent(s)
er	enantiomeric ratio
ESI	electron spray ionisation
Et	ethyl
FTase	farnesyl transferase
g	gram(s)
h	hour(s)
HMBC	heteronuclear multiple bond coherence
HMPA	hexamethylphosphoramide
HMQC	heteronuclear multiple quantum coherence
HOBT	1-hydroxybenzotriazole
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
IC_{50}	half maximal inhibitory concentration
IR	infra-red
J	coupling constant
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithiumdiisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
Lit.	literature
M	moles per litre
m	multiplet
M^+	molecular ion
m	*meta*
Me	methyl
mg	milligram(s)

MHz	megahertz
min	minute(s)
MIC	minimal inhibitory concentration
mL	milliliter(s)
mp.	melting point
MS	molecular sieves
MTBE	methyl *tert*-butyl ether
n	normal
*n*BuLi	butyllithium
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
Ns	nosyl
Nu	nucleophile
o	*ortho*
OMB	*ortho*-methoxybenzyl
p	*para*
PCC	pyridinium chlorochromate
pet. Ether	petroleum ether 40-60°C
Ph	phenyl
PMA	phosphomolybdic acid
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
Py	pyridine
q	quartet
R	alkyl group
R_f	retardation factor
rt	room temperature

s	singlet
sat.	saturated
sept	septet
sext	sextet
sol.	solution
t	triplet
t	tertiary
*t*BuLi	tertiary butyllithium
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxyl
TES	triethylsilyl
Tf	trifluoromethylsulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMDS	1,1,3,3-tetramethyldisiloxane
TMG	tetramethyl guanadine
TMS	trimethylsilyl
Tol	toluene
Ts	*p*-toluenesulfonyl
VCD	vibrational circular dichroism

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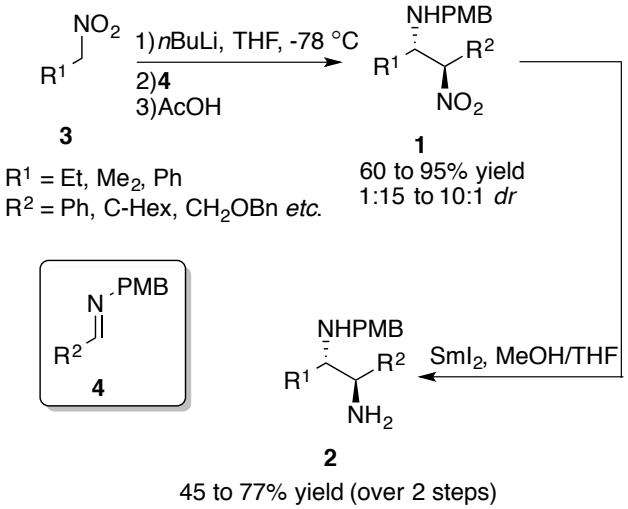
Part 1: Intramolecular Conjugate Addition Nitro-Mannich Reaction

1.0 Introduction

1.1 Nitro-Mannich Reaction

The nitro-Mannich reaction has been reported in the literature since the 1890's[1] and then in the 1900's in its primitive form.[2] This involved unselective thermal reactions, usually with the imine being formed *in situ*, but later using pre formed imines[3]. The reaction then lay dormant for a number of years, until in the late 90's the reaction was reinvestigated for its use as a means for the diastereoselective synthesis of 1,2 diamines. The first reports by Anderson *et al*. disclosed high selectivity for the *anti* diastereomers (Scheme 1).[4] Noted problems within the initial report were the stability of some of the nitroamine products, as these underwent a retro nitro-Mannich reaction on SiO_2. Reduction of the 1,2-nitroamine **1** to the 1,2-diamine **2** with SmI_2 allowed for isolation of the diamine products.



Scheme 1: Reinvestigation of the nitro-mannich reaction by Anderson *et al*.

The sense of diastereoselection of the nitro-Mannich reaction was rationalized by a Zimmerman-Traxler transition state (Figure 1), this accurately accounts for the favoured *anti* relative stereochemistry. It is thought that the *anti* diastereomer **1** is favoured as it does not suffer from the energetically disfavourable 1,3-diaxial interactions between R^2 and

the PMB group in the transition state **6**, while the *syn* diastereomer **5** does.

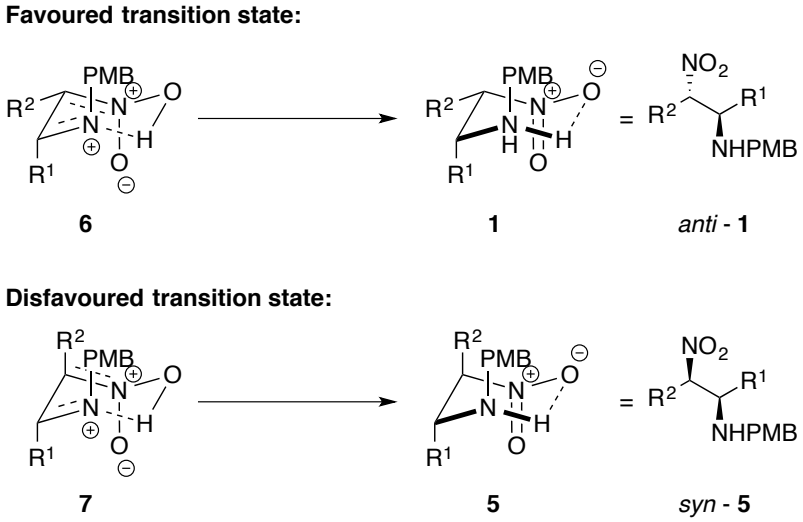
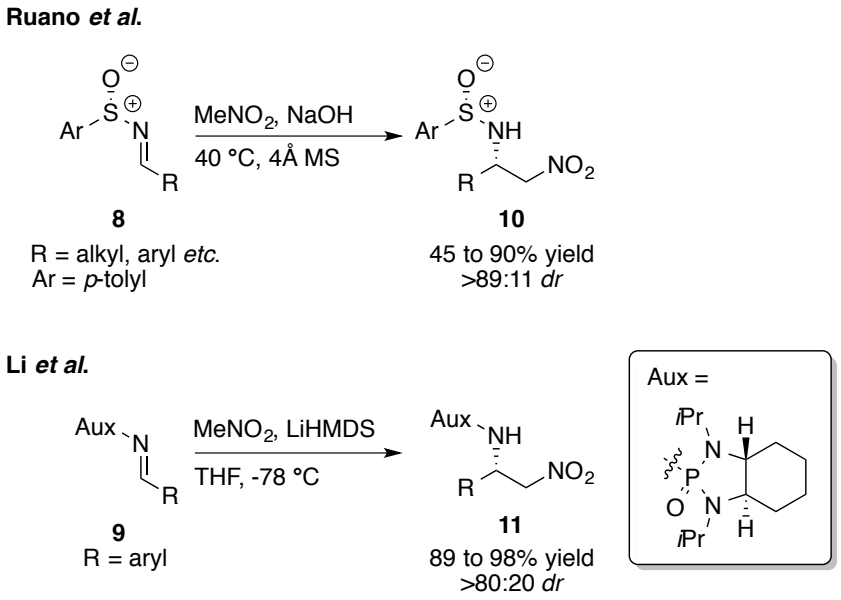


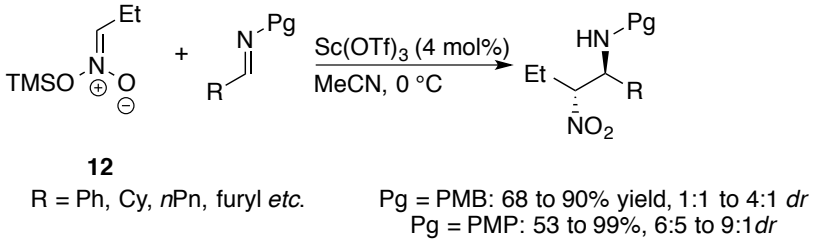
Figure 1: Proposed transition state accounting for *anti*-nitroamine **1**.

Since this modern report of the nitro-Mannich reaction there has been extensive investigation in this area, particularly as an efficient method of synthesising 1,2-nitroamines enantioselectively. Asymmetric examples of the nitro-Mannich reaction have either involved a chiral catalyst or an auxiliary approach. Two notable examples of non catalytic asymmetric nitro-Mannich reactions were reported by Ruano *et al*.[5] and another by Li *et al*.[6] These reports used chiral *N*-*p*-tolylsulfinylimines **8** or chiral *N*-phosphinoyl imines **9** to effect stereocontrol (Scheme 2).



Scheme 2: Chiral auxiliary approach to an enantioselective nitro-Mannich reaction.

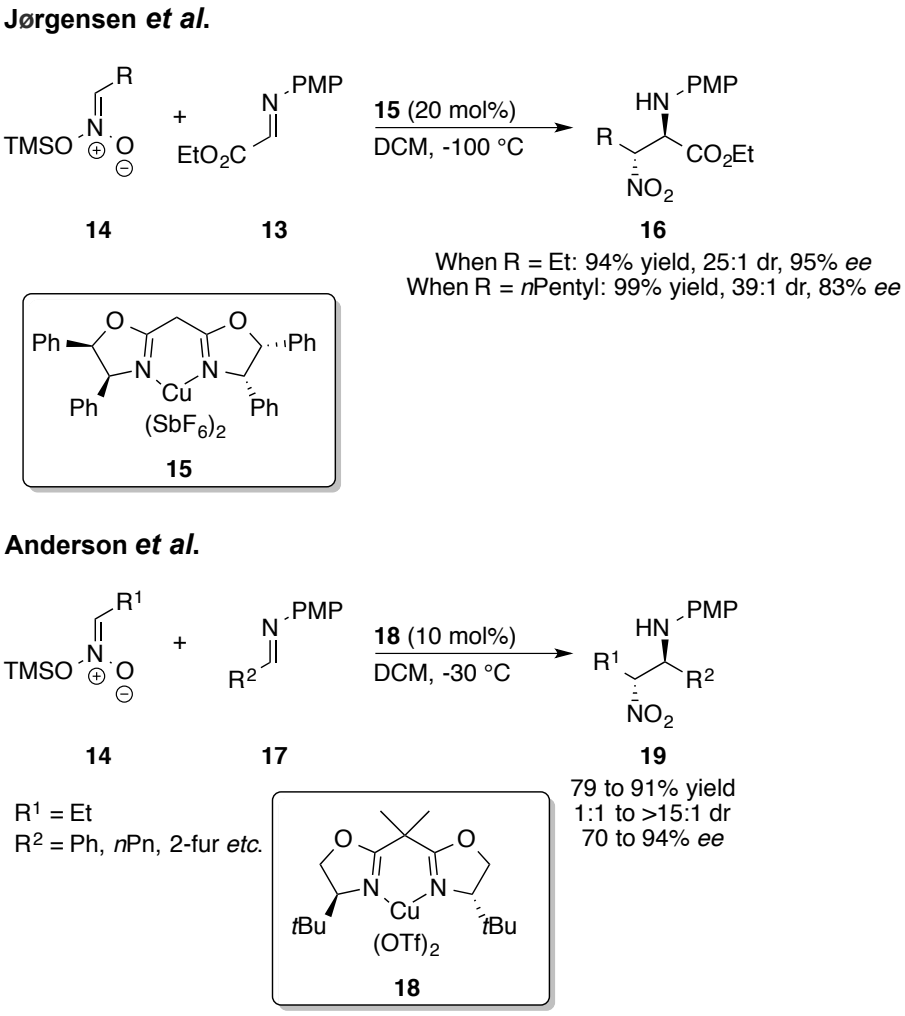
In an effort to find an asymmetric catalysed nitro-Mannich reaction, Anderson *et al*. discovered a Lewis acid catalysed nitro-Mannich reaction using silylnitronate **12** in conjunction with a scandium catalyst (Scheme 3).[7] The desired nitroamine products were made in good yields and diastereoselecitivities. During this report it was found that the PMP protecting group was more effective for diastereocontrol than the PMB protecting group. Later developments by Anderson *et al*. replaced $Sc(OTf)_3$ with $Cu(OTf)_2$ or $Ti(O\textit{i}Pr)_4$.[8]



Scheme 3: Lewis acid catalysted nitro-Mannich reaction.

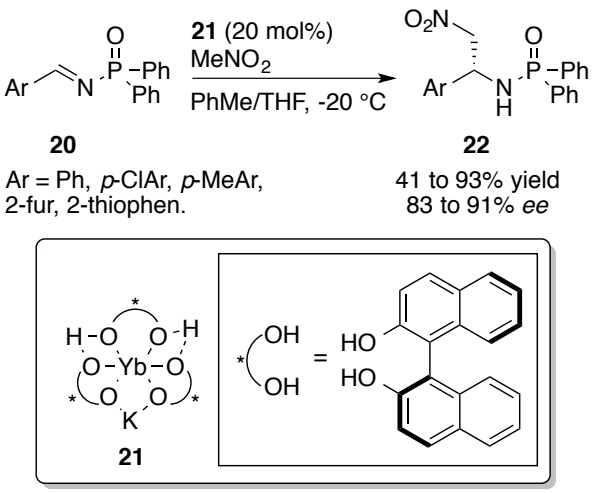
The first catalytic asymmetric example of this strategy was described by Jørgensen *et al*. While the diastereo and enantioselectivites were very good, the chemistry was restricted to the glyoxyl imine **13** (Scheme 4).[9]

This methodology was extended with a lower catalyst loading and greater substrate scope by Anderson *et al*.[10]



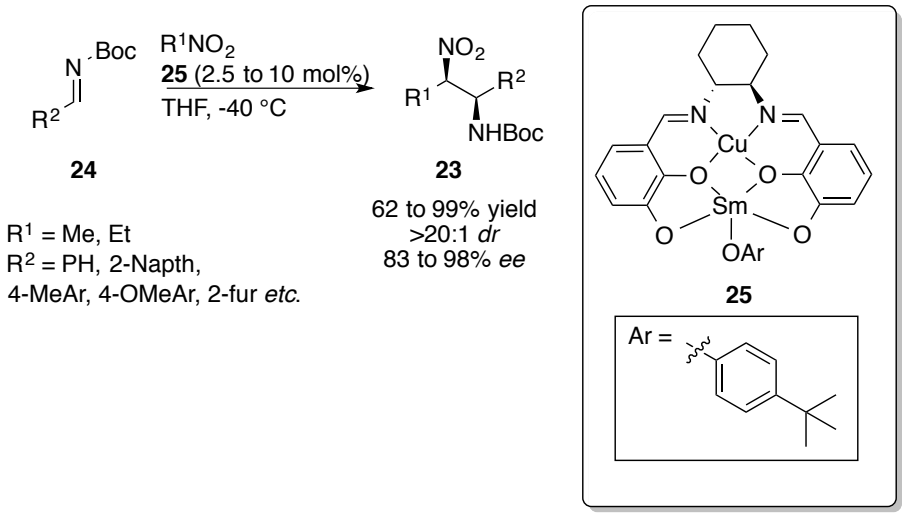
Scheme 4: Copper catalysed nitro-Mannich reaction using silyl-nitronates.

Another example of an enantioselective nitro-Mannich reaction is the heterobimetallic catalysed nitro-Mannich reaction. Pioneering work by Shibasaki *et al*. has demonstrated that heterobimetallic complexes can catalyse the nitro-Mannich reaction with high yields and with good diastereo and enantioselectivities (Scheme 5).[11]



Scheme 5: Heterobimetallic catalysed nitro-Mannich reaction.

Further work by Shibasaki *et al*. has demonstrated that certain complexes can lead to formation of the usually disfavoured *syn*-diastereomer **23** (Scheme 6).[12] This work remains one of the few examples of *syn*-selective nitro-Mannich chemistry.[13]

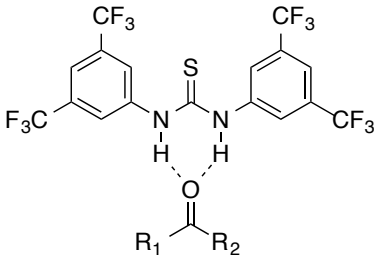


Scheme 6: *Syn*-selecive nitro-Mannich reaction.

More recently the nitro-Mannich reaction and other organic transformations have been performed using organocatalysis, particularly through the use of bifunctional thiourea catalysts.[14] These transformations allow 1,2-nitroamines to be made in high yields, stereoselectivity and frequently without inert atmospheres.[15]

1.2 Thiourea Organocatalysis Overview and Principles

The general mechanistic consensus of thiourea catalysis is the "partial protonation" of an electron rich functional group, whereby the two hydrogens on the thiourea bind to a Lewis basic site in a clamp like fashion. This mechanism can be viewed as analogous to epoxide hydrolase's mechanism of action within biology (Figure 2).[16]



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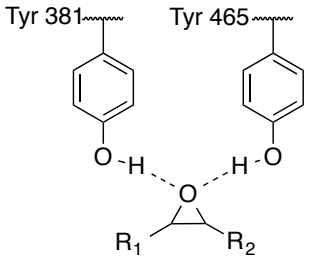

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Figure 2: Lewis acidic properties of thioureas and their counterpart in nature.

This theory has been supported by NMR molecular recognition studies, DFT calculations and reports that ureas may co-crystalize with oxygen containing molecules.[17] The hydrogen bonding strength can be measured by comparison of the pK_a of the urea or thiourea moiety; there is a clear correlation that installation of aryl groups on the urea and the replacement of oxygen for sulfur has a pronounced effect on the pK_a and in turn on binding affinities (Figure 3).[18]

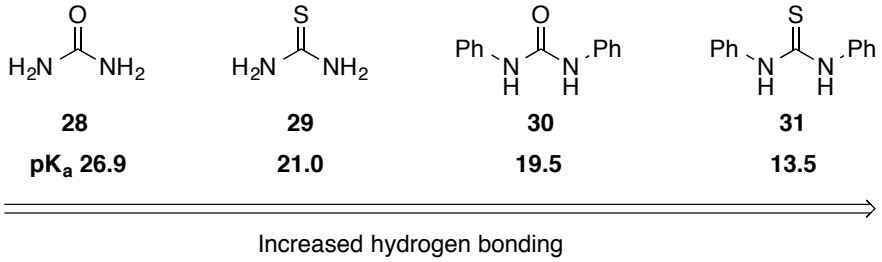


Figure 3: pK_a values of urea and thiourea derivatives.

Another effect of replacing a urea with a thiourea moiety is the decreased propensity for self-aggregation. Ureas and thioureas have multiple different binding modes: single hydrogen bonding, double hydrogen bonding and self-recognition, with the desired effect being double hydrogen bonding (Figure 4). Thioureas have a lower propensity for self-recognition than ureas; Panunto *et al*. proposed that this is due to the strength of aryl C-H interactions with the oxygen or sulfur moiety, as sulfur has stronger interactions with the C-H group, it makes the sulfur a worse hydrogen bond acceptor and so less likely to hydrogen bond to another thiourea.[19] The decreased potential for self-recognition with thioureas makes them more likely to bind to the substrate and increase catalytic turnover.

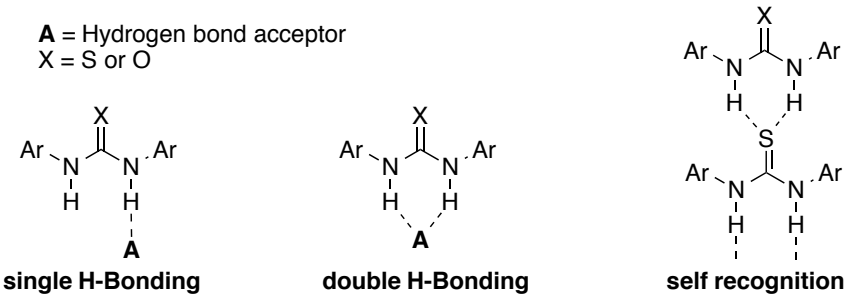


Figure 4: Different binding modes between ureas and thioureas.

Studies had shown that the efficacy of the catalyst was further increased by modification of the aryl groups. It was found that the introduction of the trifluoromethyl group on aryl thioureas increased the potency greatly. The position of the trifluoromethyl group has been examined; it was found that CF_3 groups on the *ortho* position lead to steric hindrance and *para* substitution leads to less activity than being placed on the *meta* position. Multiple factors contribute to the increase in activity;[20] the strongly electron withdrawing groups increase the acidity of the N-H bond and also the catalyst is rigidified by S-H interactions between the thiourea and the aryl hydrogens (Figure 5).[21]

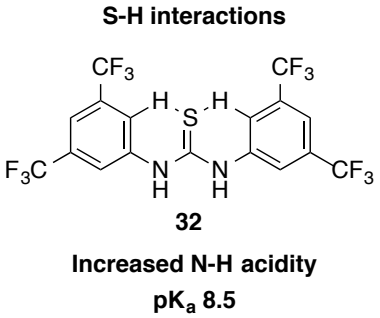


Figure 5: Effect of CF_3 introduction in thioureas.

Asymmetric reactions involving thioureas can be achieved by replacement of one of the aryl groups with chiral fragment. The source of chirality has usually been derived from an amino acid or Cinchona alkaloid but Schiff bases and alcohols may also be present (Figure 6).[21]

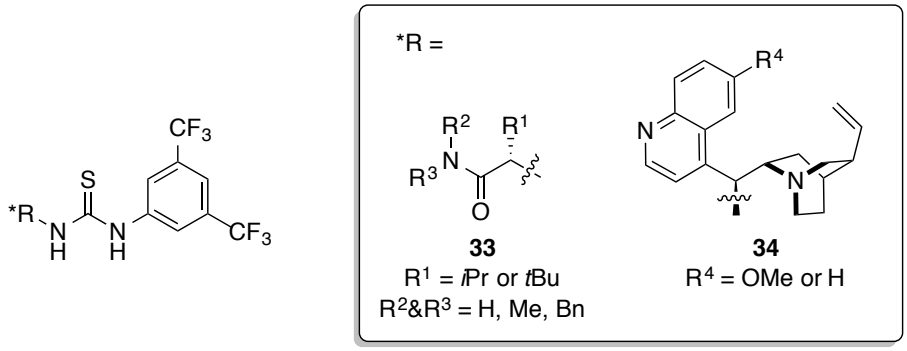
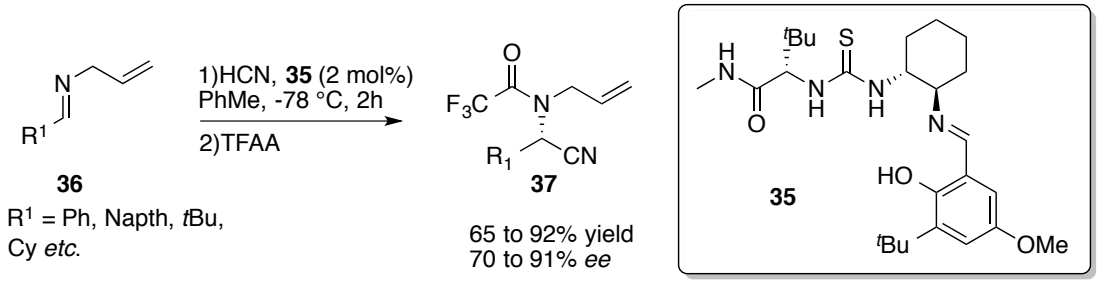


Figure 6: Frequently used chiral scaffolds on chiral thiourea catalysts.

The use of thiourea organocatalysts in organic synthesis was relatively dormant until the discovery by Jacobsen *et al*. that thiourea **35** was an effective catalyst for the asymmetric Strecker reaction (Scheme 7).[22] This has led to a dramatic increase of reported thiourea analogues and their application into a variety of reactions.



Scheme 7: Jacobsen's initial thiourea organocatalysed reaction.

The high yields and good enantioselectivity demonstrate the power of organocatalysis as a method of doing asymmetric synthesis. Prior to these reports asymmetric synthesis had previously been dominated by metal-catalysed reactions. There are also other organocatalysts that have similar mechanisms of action, for example squaramide-derived organocatalysts such as **38**[23] (Figure 7), but the use of thioureas remains dominant in the literature.

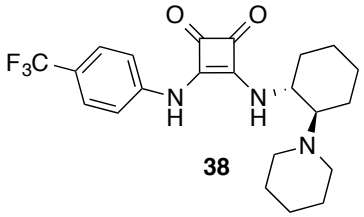
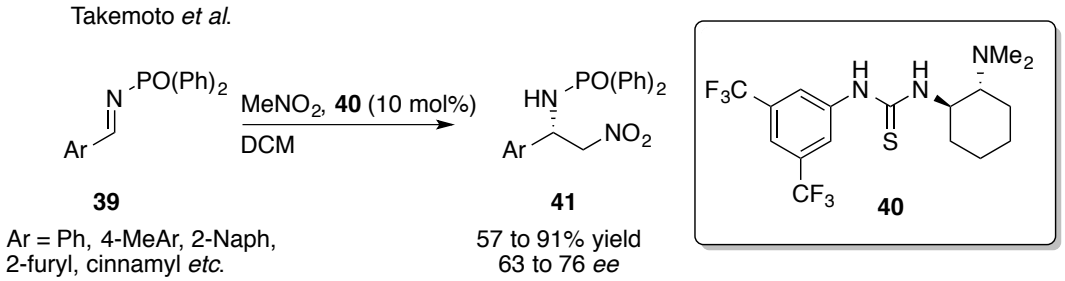


Figure 7: Rawal's squaramide derived organocatalyst.

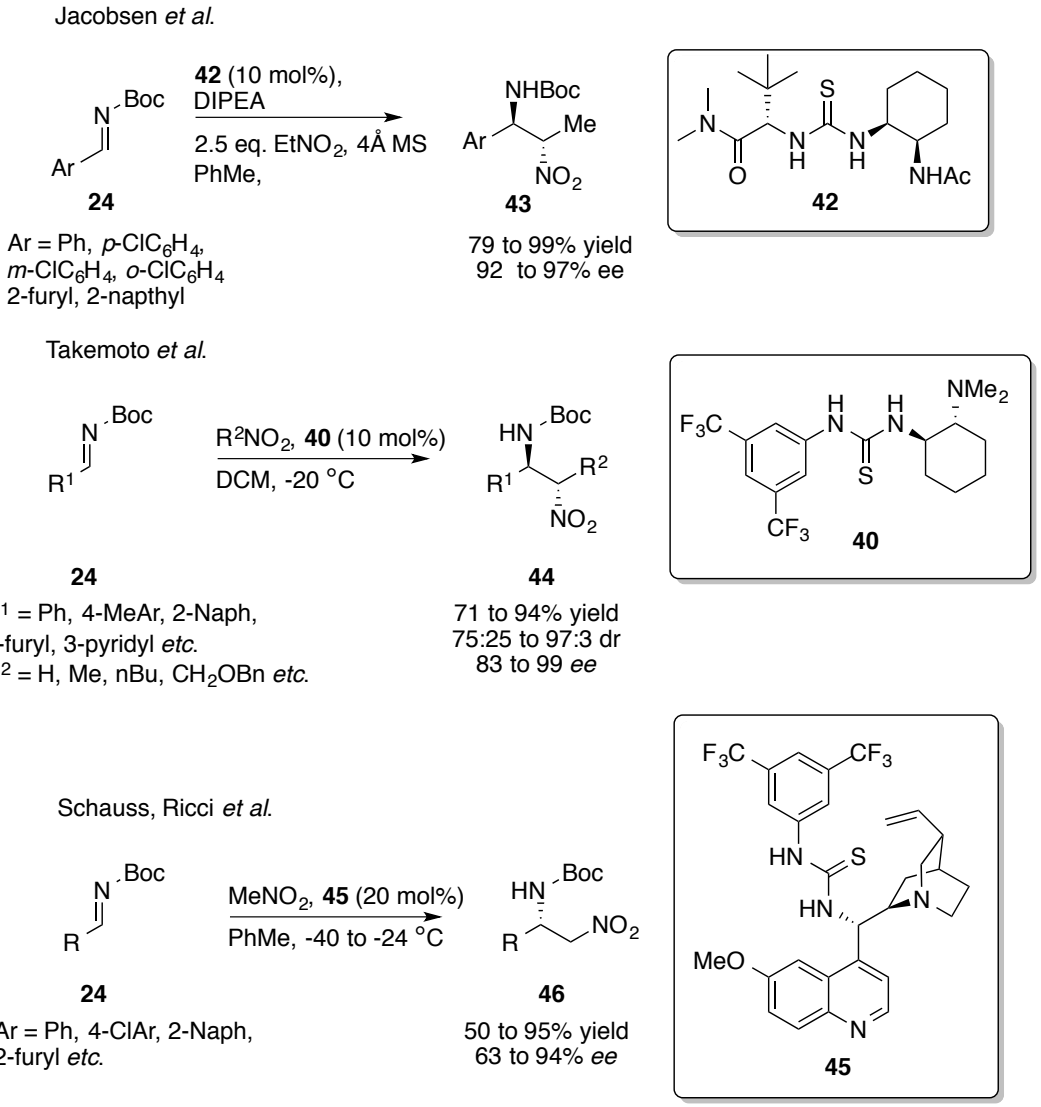
1.3 Thiourea Organocatalysed Nitro-Mannich and Related Reactions

The nitro-Mannich reaction has been reported by many groups to be catalysed by thiourea organocatalysts with good enantio and diastereocontrol. The earliest report of such a reaction was described by Takemoto *et al*. They described the nitro-Mannich reaction between *N*-phosphoryimine **39** and nitromethane (Scheme 8).[24]



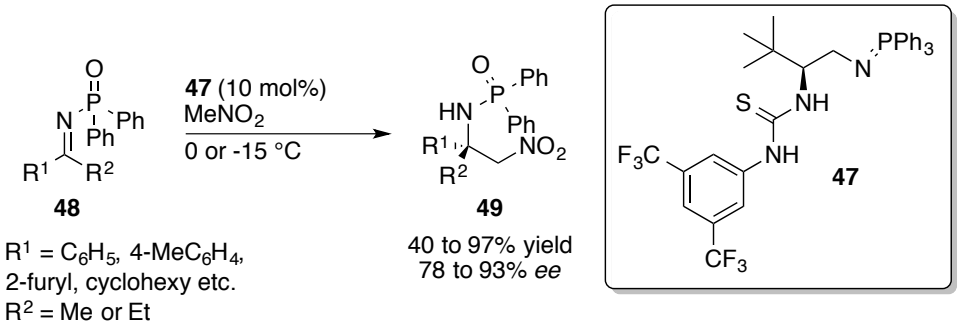
Scheme 8: Organocatalysed nitro-Mannich reaction.

Since then many groups have reported similar reactions, showcasing their modified catalysts. Disappointingly, little progress has been made on more challenging substrates or increased scope, just modification of the imine protecting groups and increased *dr*[25] or *ee* (Scheme 9).[14]



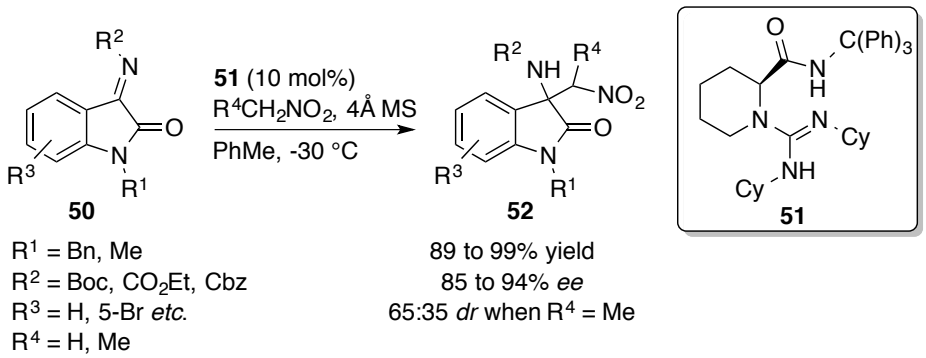
Scheme 9: Selected reports of thiourea catalysed nitro-Mannich reactions.

In an effort to broaden the synthetic utility of the organocatalytic nitro-Mannich reaction, Dixon *et al*. have developed a class of novel iminophosphorane organocatalysts **47**.[26] The structural motif includes the basic iminophosphorane moiety and the standard hydrogen-bond donor thiourea. The enhanced basicity of the iminophosphorane in comparison to tertiary amine (pKa ~22 vs. 18) allows for greater rate enhancement of the nitro-Mannich reaction and a solution to unreactive ketimines in the nitro-Mannich reaction (Scheme 10). A disappointing limitation is that nitromethane was the only reported nucleophile, so no diastereoselective examples were reported.



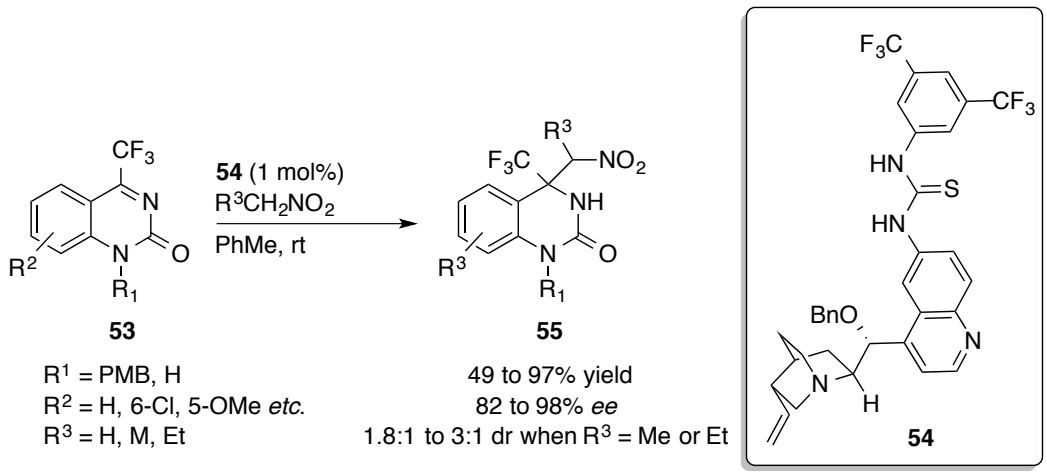
Scheme 10: Iminophosphorane based catalyst for the nitro-Mannich reaction.

Other organocatalytic nitro-Mannich reactions involving ketimines as substrates have been scarce; one example is the chiral guanidine catalysed nitro-Mannich addition of nitromethane or nitroethane to ketimines **50** derived from isatins as reported by Feng *et al*. (Scheme 10).[27] This reaction occurs in high yields and enantioselectivities, but the diastereoselectivity was poor.



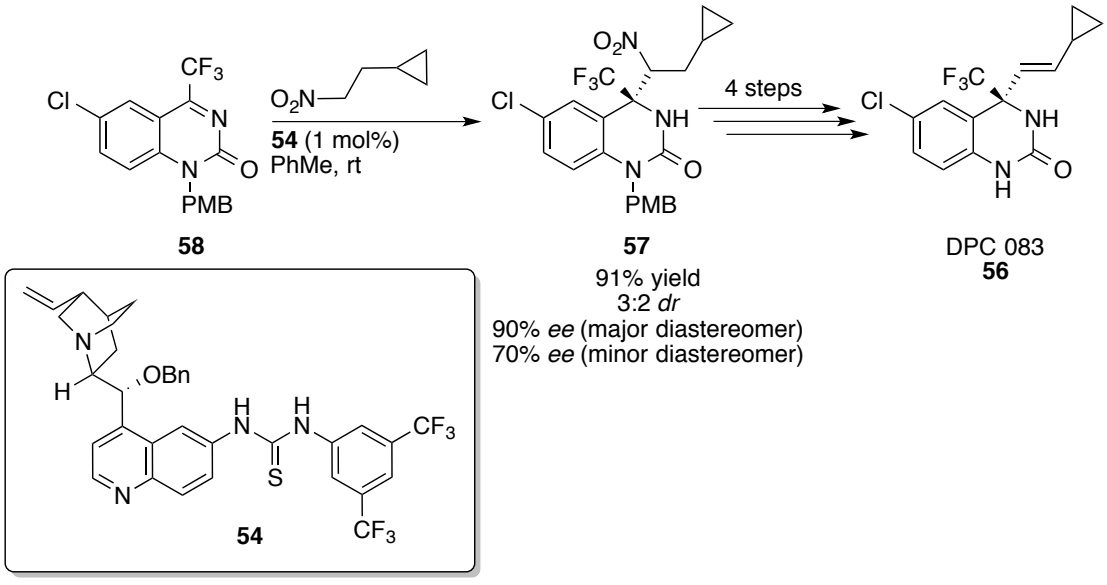
Scheme 10: Enantioselective addition of nitroalkanes to isatin derived ketimines.

Another limited example is the organocatalysed addition of nitroalkanes to trifluomethyl-substituted ketimines **53** as described by Wang *et al*. (Scheme 11). The yields were usually good to very good and the enantioselectivities were usually very good.[28]



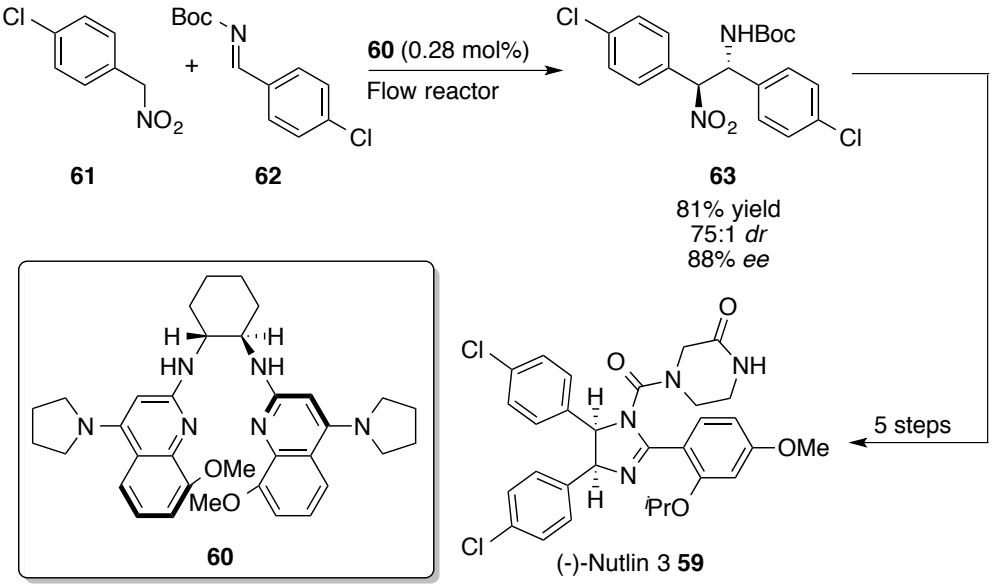
Scheme 11: Enantioselective addition of nitroalkanes to trifluoromethyl ketimines.

The same report demonstrated the synthetic utility of their methodology by describing an efficient asymmetric synthesis of the HIV drug DPC 083 **56** (Scheme 12). The nitroamine **57** was made in a high yield, but with a relatively low *dr*, but this was unimportant as both diastereomers were carried through the synthesis.



Scheme 12: Asymmetric synthesis of DPC 083 by a nitro-Mannich reaction.

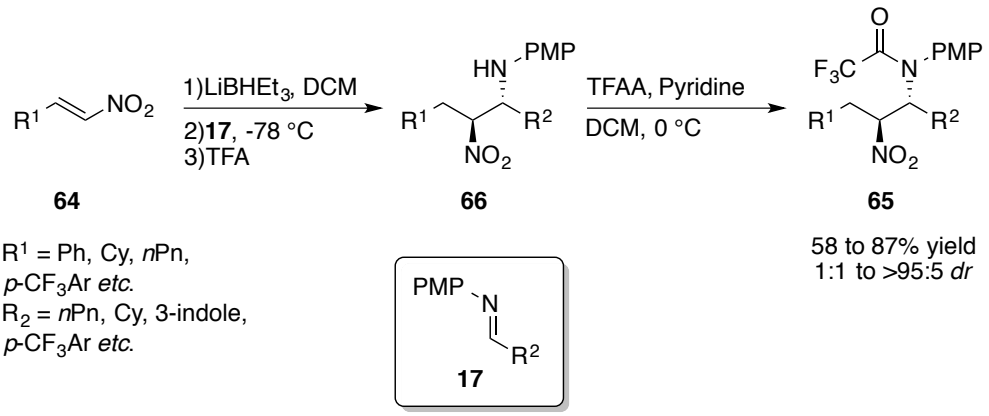
While there is still scope for developing the nitro-Mannich reaction further, it has recently been adopted in an industrial setting.[29] A process scale synthesis of (-)-Nutlin 3 **59** was reported by Johnson *et al*. (scheme 13), this report follows on from their work using chiral proton catalyst **60** to make 1,2-diamines.[30]



Scheme 13: Process scale synthesis of Nutlin-3.

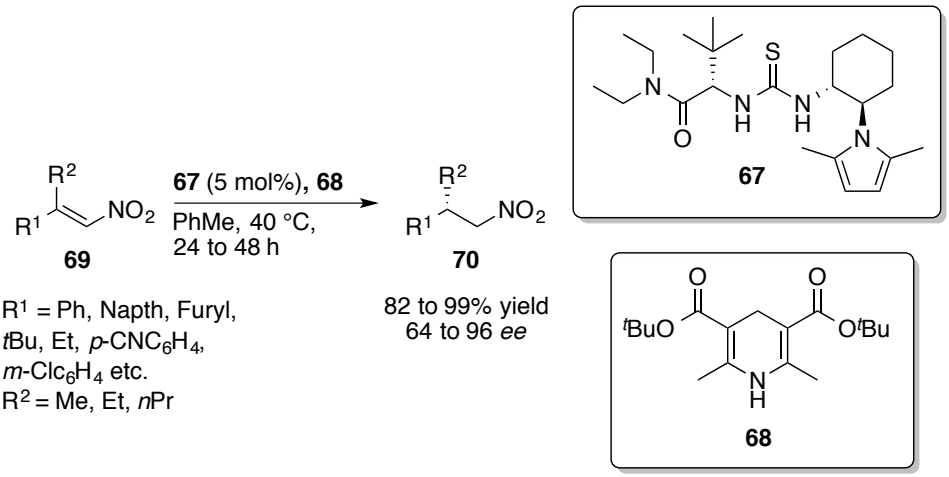
1.4 Organocatalytic Conjugate Addition Nitro-Mannich Reaction

As the nitro-Mannich reaction was usually limited to examples using nitromethane or other commercially available nitroalkanes, work by Anderson *et al*. expanded the reaction to use nitroalkenes **64** as masked nitronates in the nitro-Mannich reaction, simply by addition of a hydride source (Scheme 14). A benefit to this strategy is that the nitroalkene substrate can be made easily by a Henry reaction with nitromethane and an aldehyde.[31] During this time Anderson *et al*. had also found that the nitroamine was isolable and could be purified by column chromatography if protected as the *N*-trifluoroacetamide **65**.



Scheme 14: Use of nitroalkenes in a diastereoselective nitro-Mannich reaction.

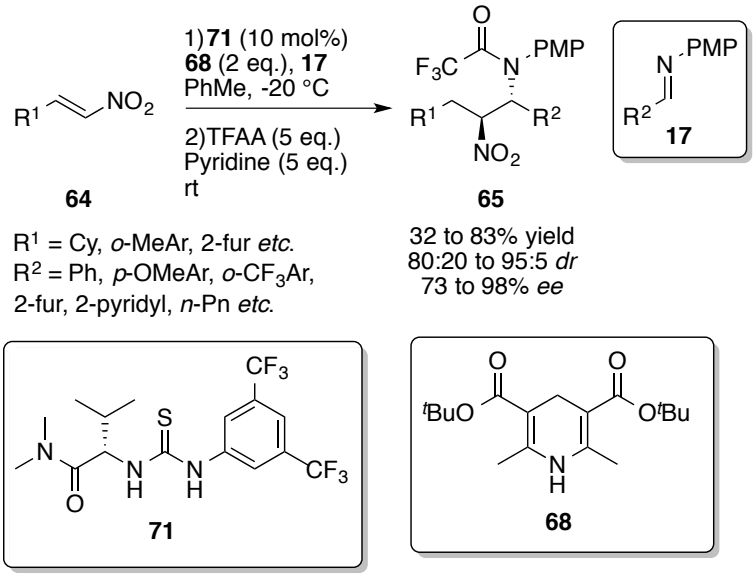
The organocatalytic generation of nitronates has previously been reported in the literature, but the nitronate had not been intercepted for a tandem nitro-Mannich reaction. List *et al*. had described the use of thiourea catalyst **67** with Hanzstch ester **68** as a transfer hydrogenation agent in the reduction of nitroalkenes **69** to enantioenriched nitroalkanes **70**. This gave very good stereocontrol with good substrate scope (Scheme 15).[32]



Scheme 15: Organocatalytic reduction of nitrostyrenes reported by List *et al*.

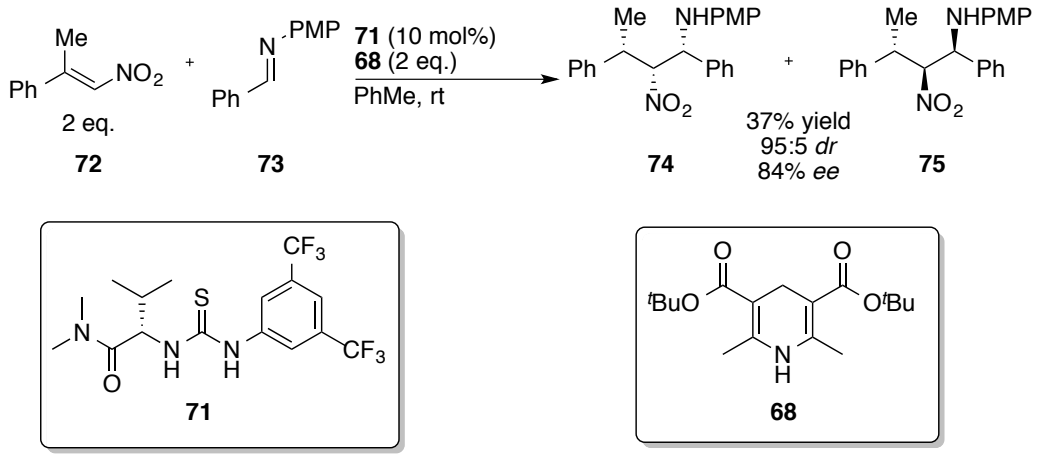
This transfer hydrogenation method was then modified by Anderson *et al*. to perform a tandem reduction/nitro-Mannich reaction using thiourea catalyst **71** and Hantzsch ester **68**. The nitroamine products were formed

in high diastereo and enantioselectivities as the *N*-trifluoroacetamide **65** (Scheme 16).



Scheme 16: Tandem organocatalytic reductive nitro-Mannich reaction.

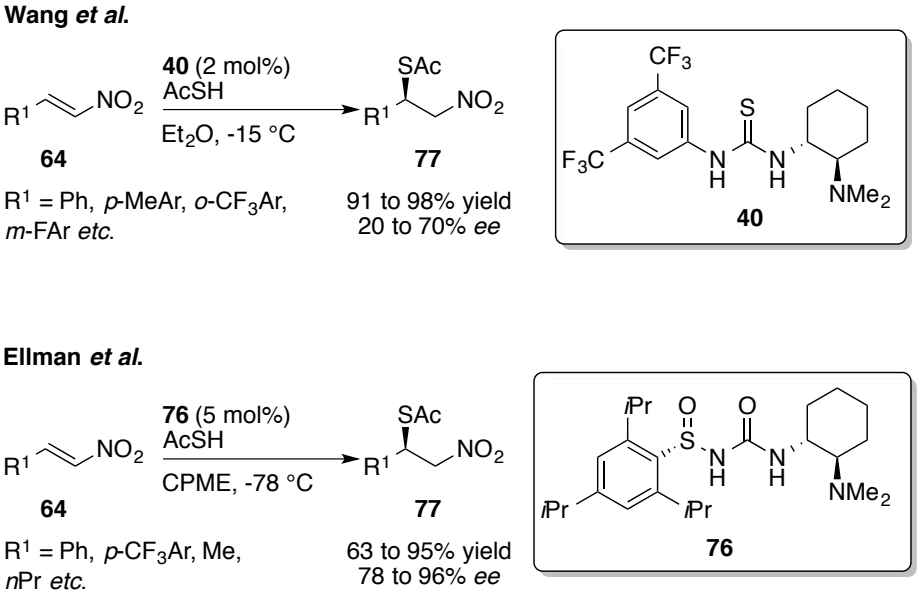
The same report also demonstrated the ability to form three contiguous-stereocenters in one-pot, catalytically (Scheme 17).[33]



Scheme 17: Tandem reduction/nitro-Mannich reaction.

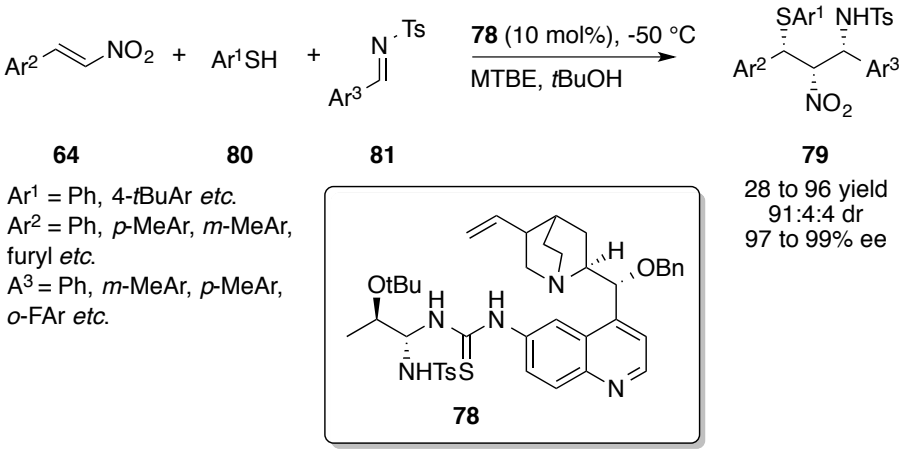
The Michael addition to nitrostyrenes is not limited to hydride nucleophiles, there have been reports of organocatalytic Michael additions using other nucleophiles[34] such as indoles,[35] oximes[36] and amines.[37] The organocatalytic addition of thioacetate to a nitrostyrene

has been described by Wang *et al*.[38] and Ellman *et al*., though both methods had to be performed at low temperatures in order to supress an uncatalysed racemic reaction. Ellman *et al*. managed to achieve high enantioselectivities using the unusual *N*-sulfinylurea **76** as a catalyst (Scheme 18).[38, 39]



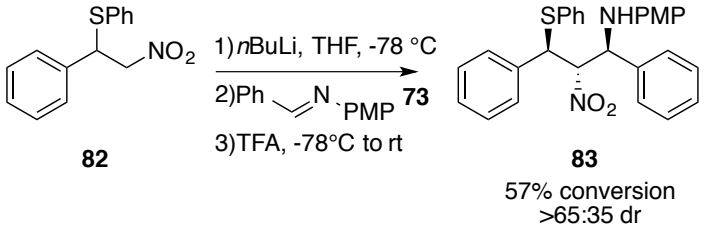
Scheme 18: Organocatalysed thio-Michael reaction.

Peng *et al*. applied the organocatalysed addition of thiols to nitrostyrenes to perform a tandem Michael/nitro-Mannich reaction. The tandem reaction using thiourea **78** provided the *syn*,*syn* nitroamine **79** in good diastereoselectivity and excellent enantioselectivities (Scheme 19).[40] This work is a continuation of Peng *et al*.'s thio-Michael/Mannich procedure that they had previously developed.[41]



Scheme 19: Thio-Michael/nitro-Mannich cascade.

The *syn*,*syn* stereochemistry reported by Peng *et al*. is in contrast to the use of β-thionitroalkane **82** in the nitro-Mannich reaction as reported by Anderson *et al*. This report gave the *anti*,*anti* diastereomer **83** in a low conversion and *dr* (Scheme 20).[42] This approach demonstrates that while the organocatalysed nitro-Mannich reaction is a powerful method of making 1,2-nitroamines, it is complementary to the uncatalysed variant, not a replacement, as frequently different stereoselectivities are observed between the two.



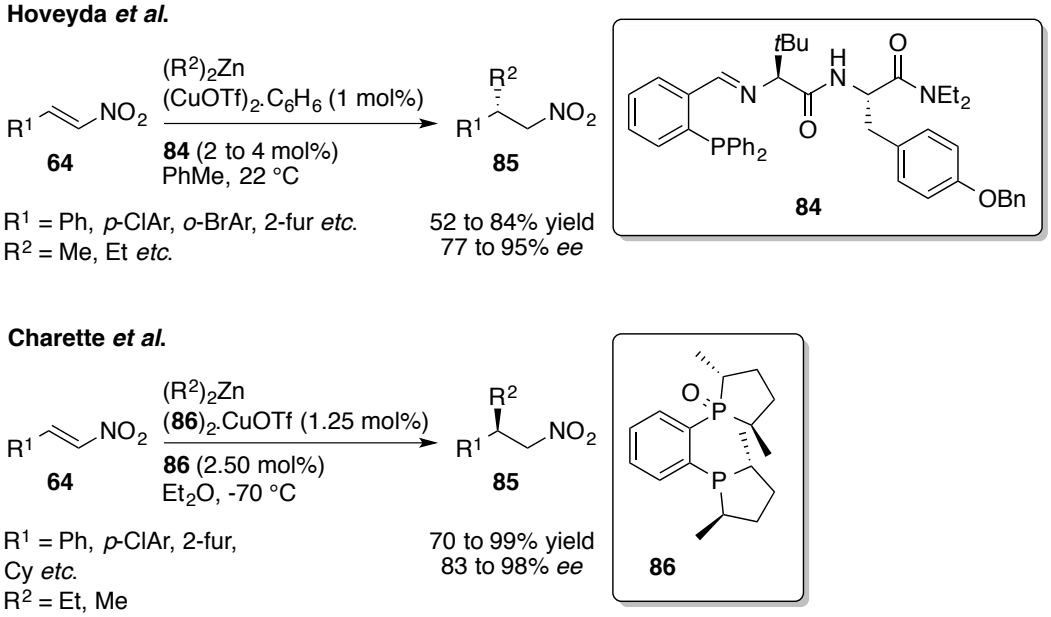
Scheme 20: Synthesis of *anti*,*anti*-nitroamine **83**.

1.5 Use of Dialkylzincs in the Nitro-Mannich Reaction

While most reports of a tandem Michael/nitro-Mannich reaction involve a soft hydride or heteroatom nucleophile in conjunction with an organocatalyst, Anderson *et al*. described an alternative approach.

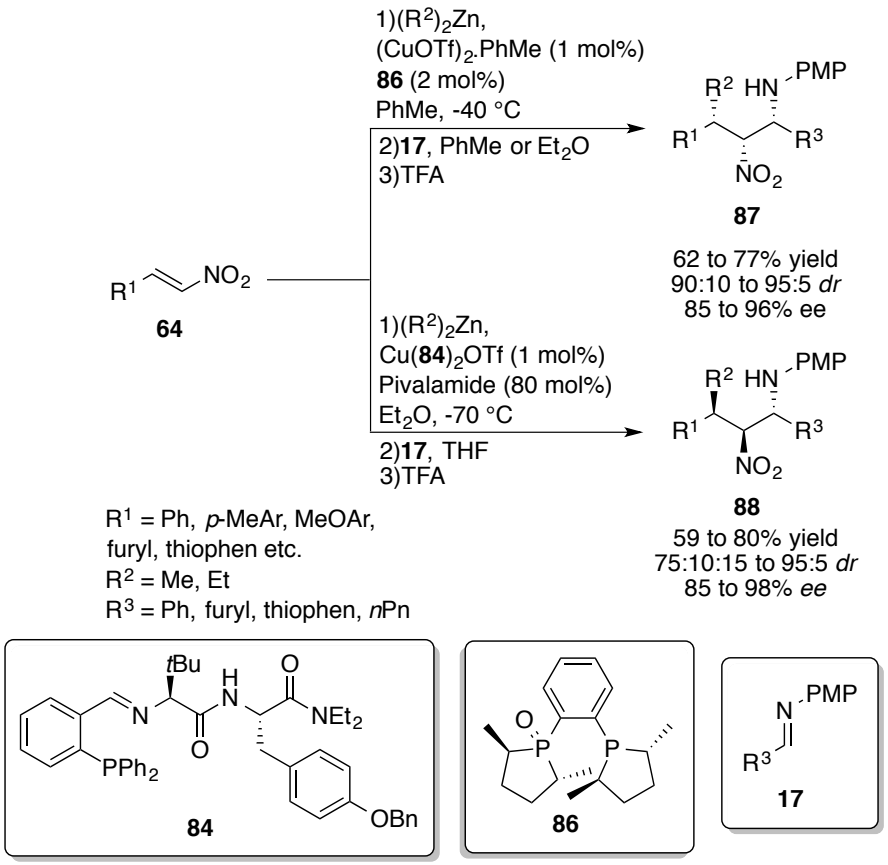
Addition of dialkylzincs to nitrostyrenes in the presence of a copper catalyst and chiral ligand has been shown to be an effective method of

making nitroalkanes containing a chiral center β to the nitro group. Despite this, the nitronate intermediate was never intercepted for a Henry or nitro-Mannich reaction (Scheme 21). [43]



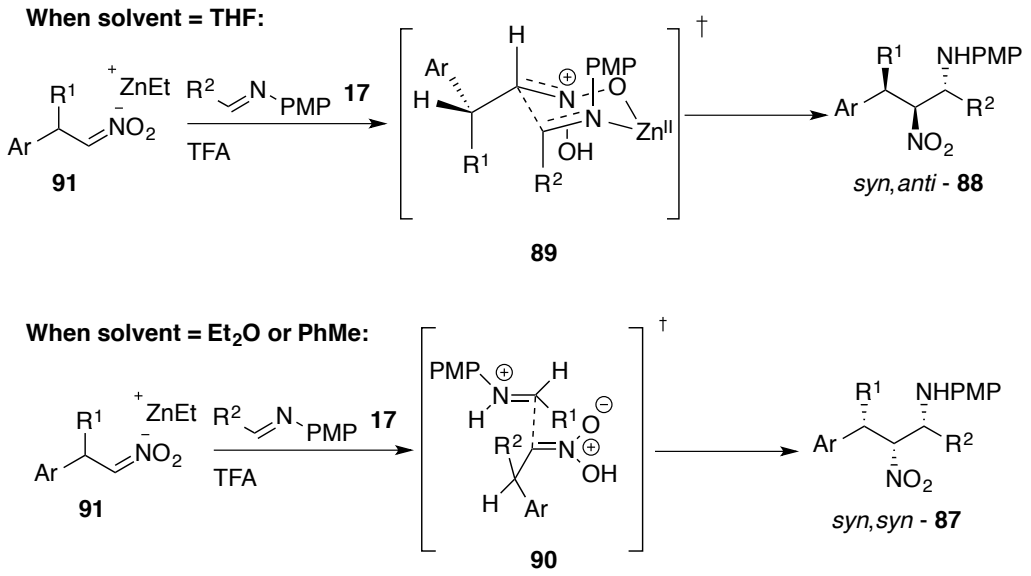
Scheme 21: Enantioselective addition of dialkylzincs to nitroalkenes.

Anderson *et al*. used these reports and developed a Michael/nitro-Mannich reaction that gave either the *syn*,*anti* or *syn*,*syn* diastereomers depending on the solvent used (Scheme 22).[44]



Scheme 22: Enantioselective synthesis of *syn*,*syn* or *syn*,*anti* nitroamines.

This remarkable shift in selectivity is attributed to the solubility of zinc trifluoroacetate made during the reaction. In a Lewis basic solvent such as THF the $Zn(CF_3COO)_2$ product is soluble and so upon addition of an imine and TFA a nitro-Mannich reaction occurs *via* a Zimmerman-Traxler transition state **89** with complexation between the Zn^{II} species, the nitronate and imine. In poorly Lewis basic solvents such as Et_2O or PhMe the $Zn(CF_3COO)_2$ is insoluble and so the reaction proceeds *via* a Houk-type transition state **90** as the Zn^{II} species is not available for complexation (Scheme 23).



Scheme 23: Proposed transition states leading to either the *syn*,syn or *syn*,*anti* nitroamines.

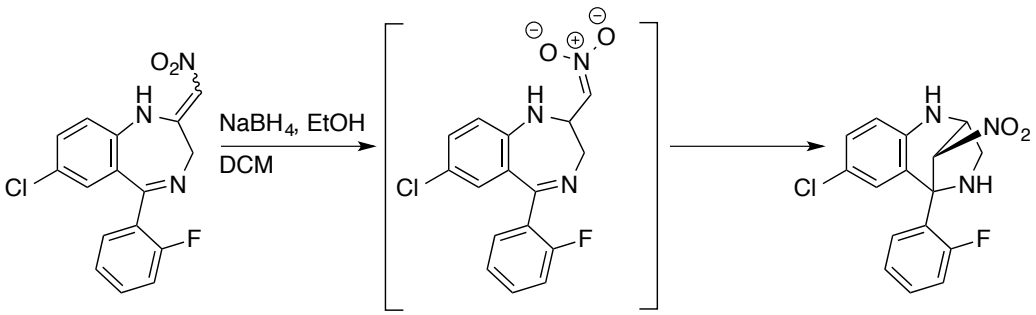
This approach provided an enantioselective synthesis of densely functionalised nitroamines, with the sense of diastereoselectivity changed by a simple solvent switch.

1.6 Stereoselective Synthesis of *N*-Heterocycles Using the Nitro-Mannich Reaction

As the nitro-Mannich reaction is an effective method to synthesise 1,2-diamines, enantioselectively, it has been successfully applied to the stereoselective synthesis of *N*-heterocycles.

1.7 Intramolecular Cyclisation Strategy

One of the first reports of the nitro-Mannich reaction and intramolecular variant was reported by Walser *et al*. who reported an unexpected cyclisation of benzodiapene **92** to give bridged *N*-heterocycle **93** (Scheme 24).[45] The authors were trying to reduce a nitroalkene to nitroalkane in the presence of an imine with $NaBH_4$, but instead they isolated the nitroamine **93**. The general mechanism is thought to be a 1,4-reduction of nitroalkene **92** to give nitronate **94** and then intramolecular attack of the imine to give nitroamine **93**.

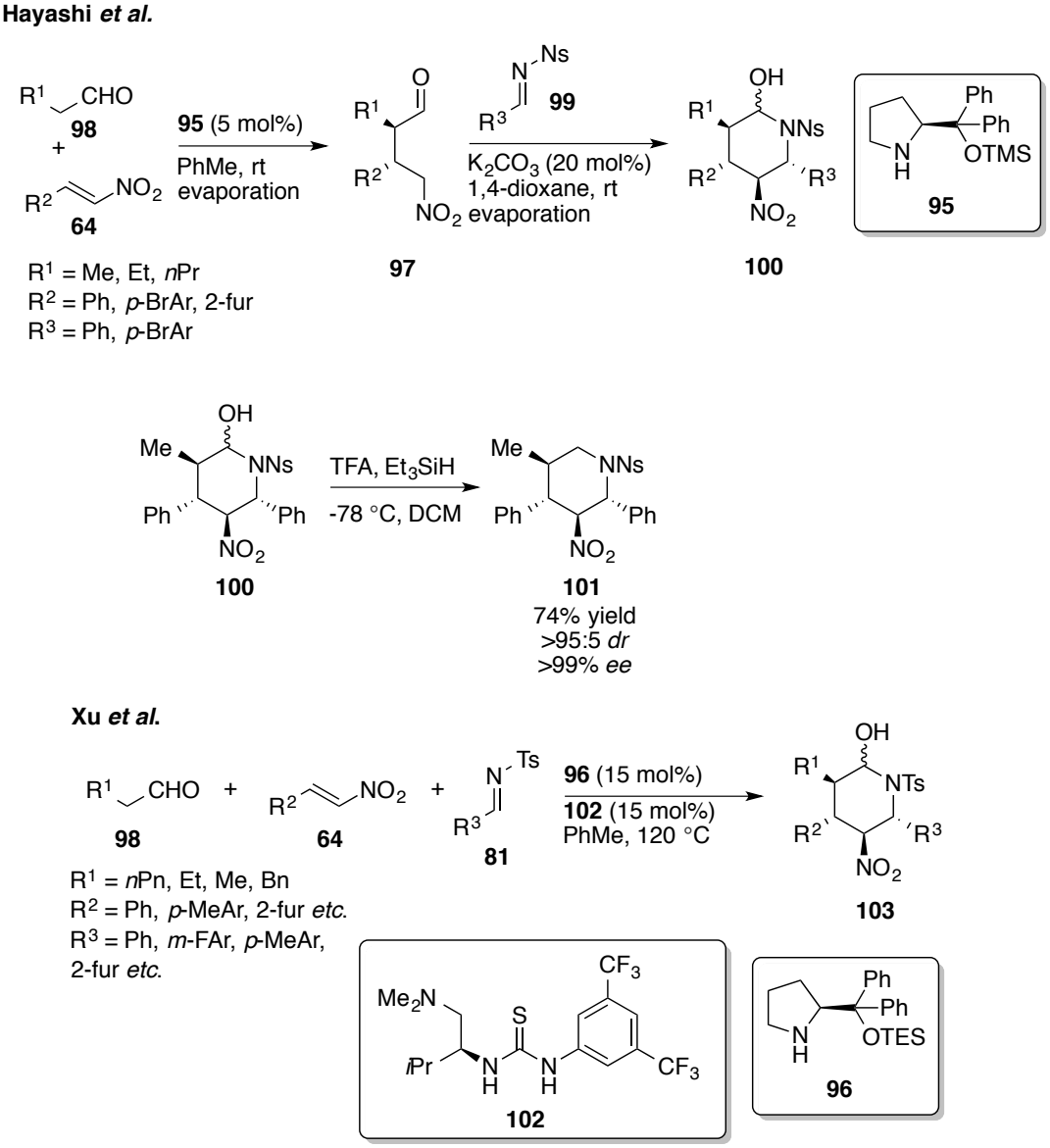


92 **94** **93**
81% yield

Scheme 24: First intramolecular conjugate addition nitro-Mannich reaction.

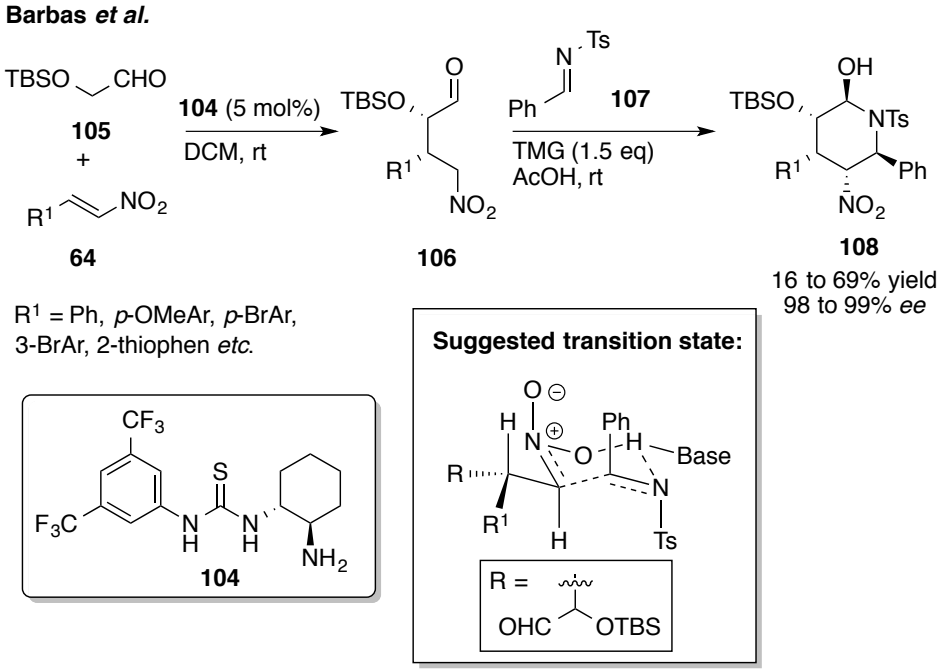
A popular use of the nitro-Mannich reaction is the synthesis of densely functionalised piperidines (Scheme 25). This tactic was investigated by Hayashi *et al*.[46] and Xu *et al*.[47] The synthetic sequence involved first the conjugate addition of an aldehyde to a nitrostyrene in the presence of catalyst **95** or **96** and then reaction of the nitroalkane product **97** with an imine. Hayashi *et al*. did not isolate the hemiaminal; instead they

displaced the hydroxyl with either an allyl, alcohol, nitrile or hydride nucleophile.



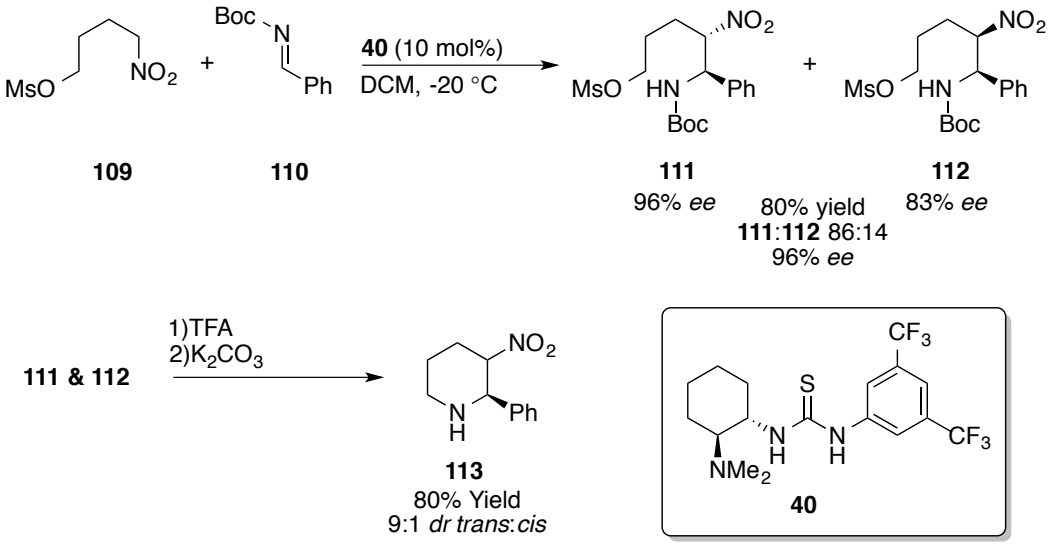
Scheme 25: Synthesis piperidine rings using an organocatalytic nitro-Mannich reaction.

Barbas *et al*. described a similar transformation using thiourea catalyst **104**, but observed a different stereoselectivity (Scheme 26).[48] They account for the relative stereochemistry by suggesting a transition state similar to that described by Anderson *et al*. in the synthesis of *syn*,*anti* ntroamines.[44]



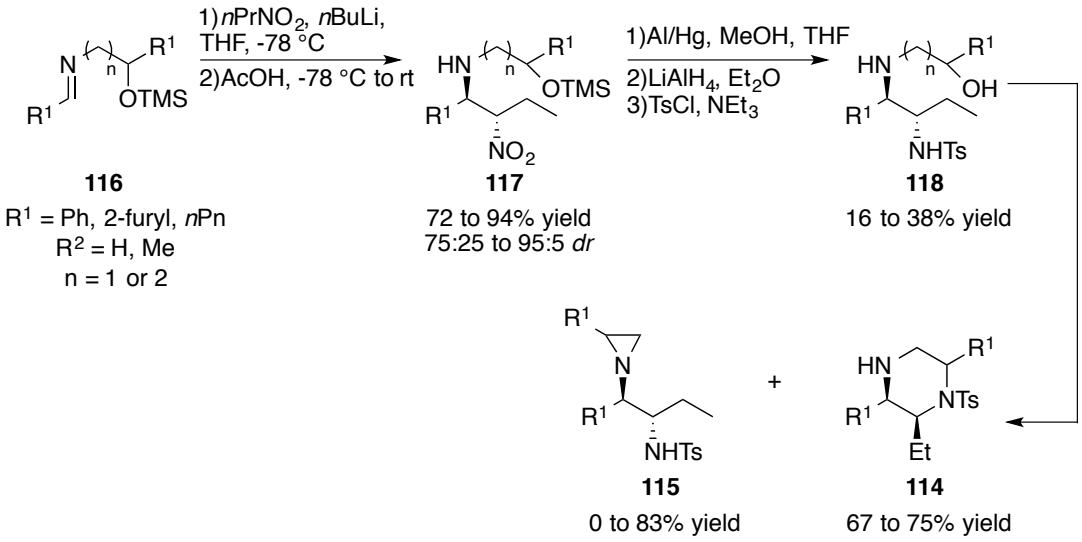
Scheme 26: Synthesis of densely functionalised piperidine **108**.

Another approach to the synthesis of piperidines was an organocatalytic nitro-Mannich reaction and then subsequent base-mediated annulation (Scheme 27). This strategy was used in the formal synthesis of (-)-CP-99,994.[49]



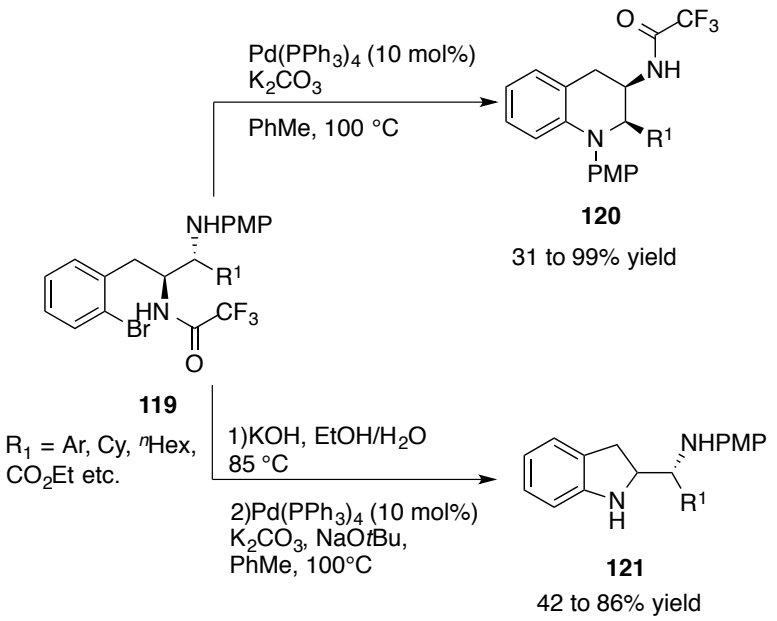
Scheme 27: Construction of piperidine **113** using a nitro-Mannich reaction/intramolecular cyclisation sequence.

Anderson *et al*. disclosed the synthesis of piperazine **114** and aziridine **115** using 1,2-diamines that were made by the nitro-Mannich reaction. These 1,2-diamines were derived from imine **116** that contained a protected alcohol and so after deprotection of the TMS protecting group an intramolecular Mitsonobu cyclisation could be performed, forming various *N*-heterocycles depending on the conditions (Scheme 28).[50]



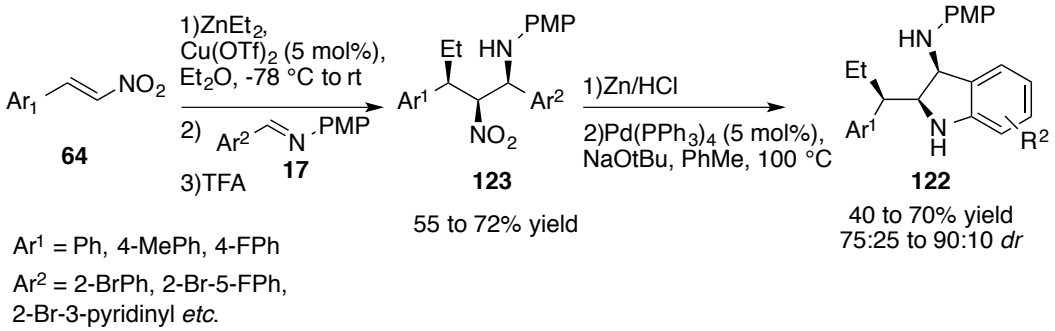
Scheme 28: Synthesis of piperazine **114** and aziridine **115** using nitroamine **117**.

Another ring closure strategy involving nitroamines is the use of the Buchwald-Hartwig reaction. Anderson *et al*. have used 1,2 diamines **119** made by a nitro-Mannich reaction for the synthesis of tetrahydroquinolines **120** and indolines **121** (Scheme 29).[51] This was done by an intramolecular Buchwald-Hartwig reaction with the choice of conditions enabling either orthogonally protected amine to react. A noted issue was the remaining PMP protecting group at the end of the synthesis, which is difficult to remove.



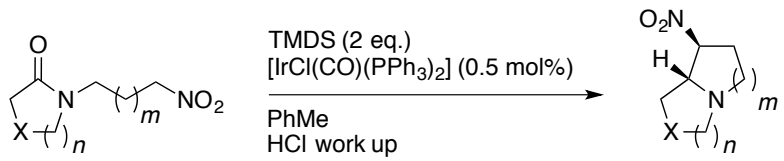
Scheme 29: Use of 1,2-diamines for heterocycle synthesis.

Similarly Anderson *et al*. later demonstrated the synthesis of densely substituted indolines **122** by combining their dialkylzinc mediated three-component nitro-Mannich reaction and the Buchwald-Hartwig reaction (Scheme 30). [52]



Scheme 30: Synthesis of indolines using a three-component nitro-Mannich reaction.

A metal catalyzed reductive nitro-Mannich cyclisation as a means to construct *N*-heterocycles has been described by Dixon *et al*. This procedure used an iridium catalyst combined with a silane reductant, giving the desired heterocycles in high yields and diastereoselectivity (Scheme 31). They then demonstrated its use by a racemic synthesis of natural product *epi*-epiquinamide[53]

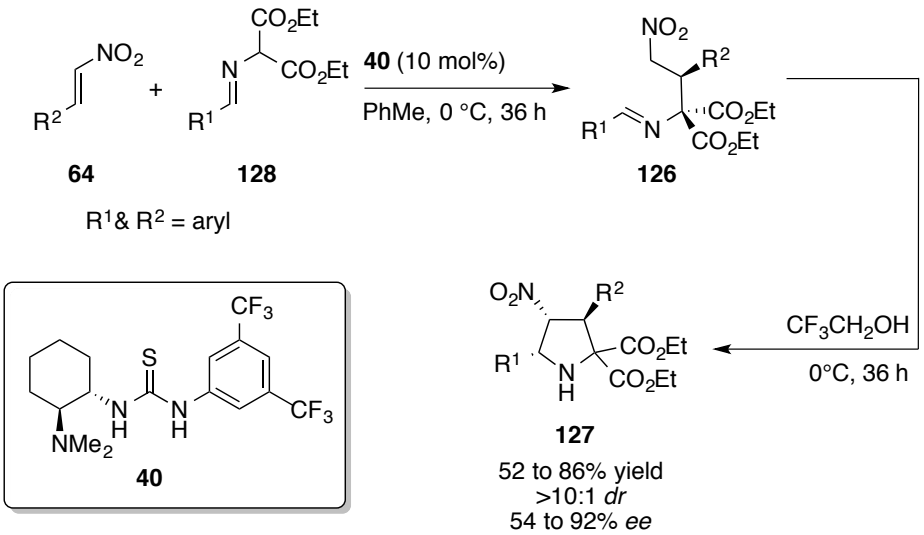


124
X = CH_2 or O
n & *m* = 0, 1, 2 or 3

125
37 to 80% yield
55:45 to >98:2 dr

Scheme 31: Iridium catalysed reductive nitro-Mannich cyclisation.

A different use of the nitro-Mannich was described by Takemoto *et al*. that involved a formal [3+2] cycloaddition of azomethine ylides to nitroalkenes (Scheme 32).[54] The reaction is thought to proceed in a step wise-manner, first a Michael addition onto the nitrostyrene **64** to give nitroalkane **126,** and then an intramolecular nitro-Mannich reaction to give the pyrrolidine **127** in good yields and with high stereoselectivity.



64 **128** **126**

R^1 & R^2 = aryl

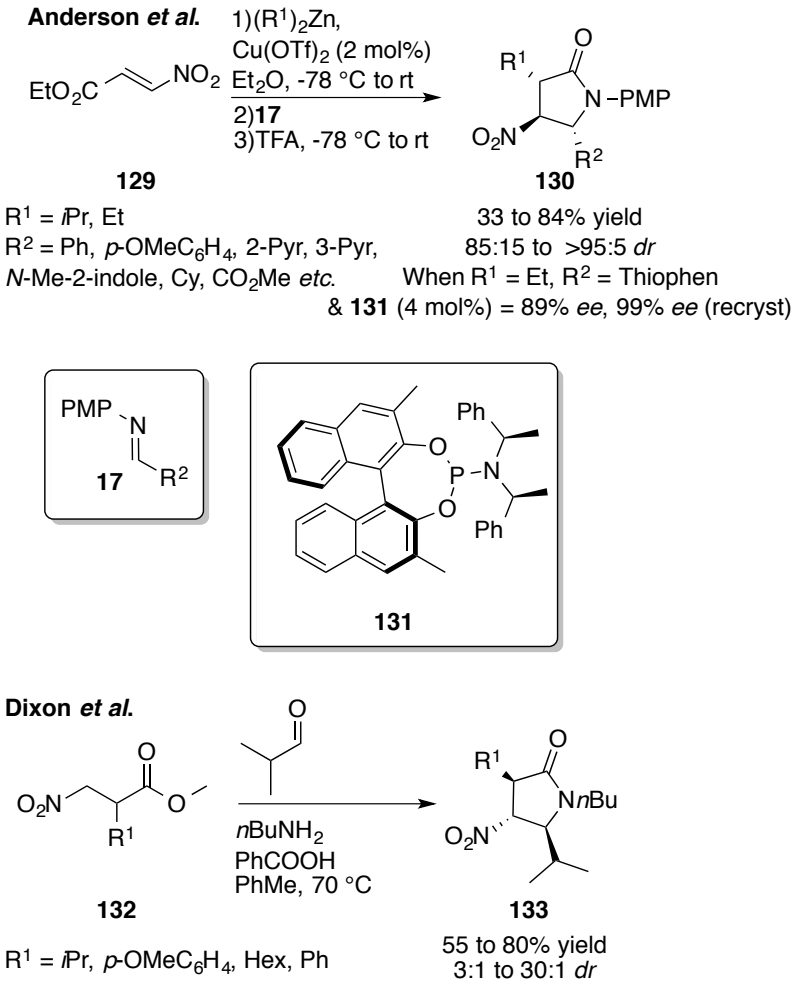
40

127
52 to 86% yield
>10:1 *dr*
54 to 92% *ee*

Scheme 32: Formal [3+2] strategy to enantioenriched piperidine **127**.

1.8 Nitro-Mannich/Lactamisation Approach to *N*-Heterocycles

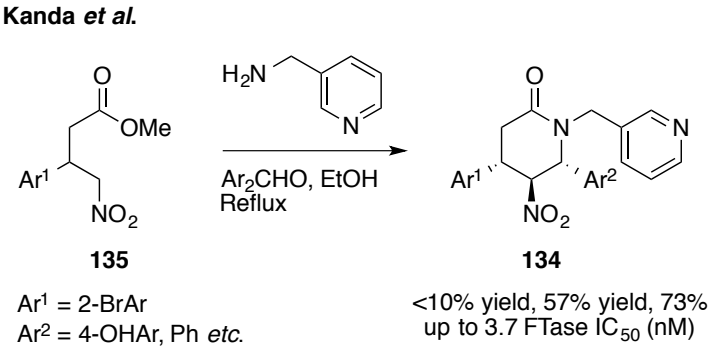
The use of a nitro-Mannich/lactamisation cascade to synthesise heterocycles has appeared to be popular. A noted advantage of this strategy is that the 1,2-nitroamine is internally protected as the cyclic amide, preventing a retro reaction. Both Anderson *et al*.[55] and Dixon *et al*.[56] have described methods for the formation of pyrrolidin-2-ones by a nitro-Mannich reaction and then intramolecular lactamisation (Scheme 33). An advantage of the method described by Anderson *et al*. is the large substrate scope and ability to control the absolute stereochemistry that is lacking in Dixon *et al*.'s variant.



Scheme 33: Intramolecular lactamisation route to heterocycles.

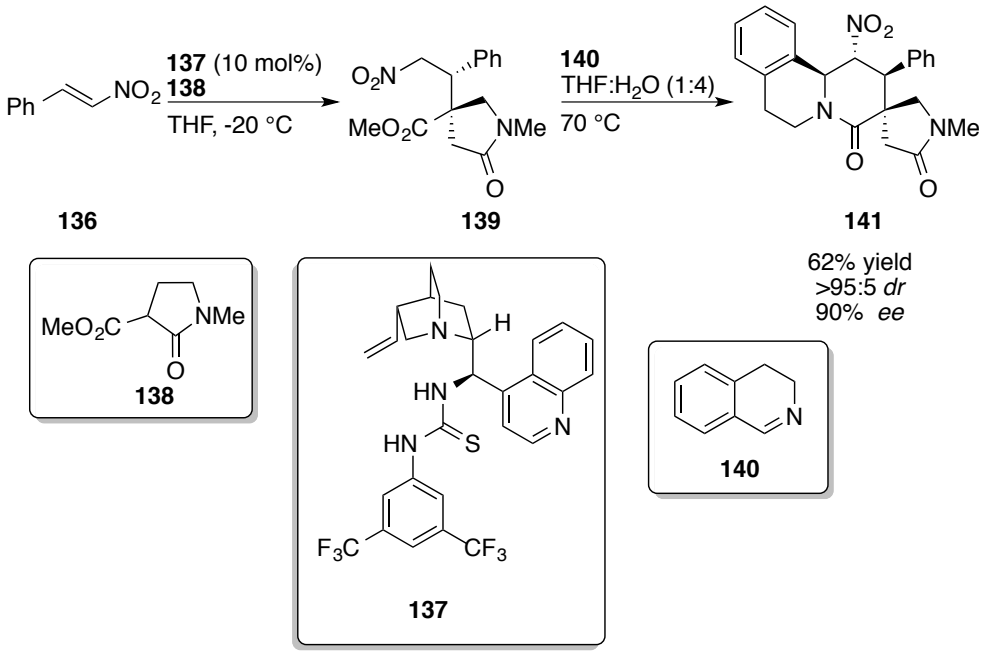
A nitro-Mannich/lactamisation cascade was first reported by Jain *et al*. to successfully synthesise piperidones in an acceptable yield.[57] It was then

used in the synthesis of densely functionalised piperidones **134** by Kanda *et al*. These piperidones were then investigated as farnesyl transferase inhibitors (Scheme 34).[58]



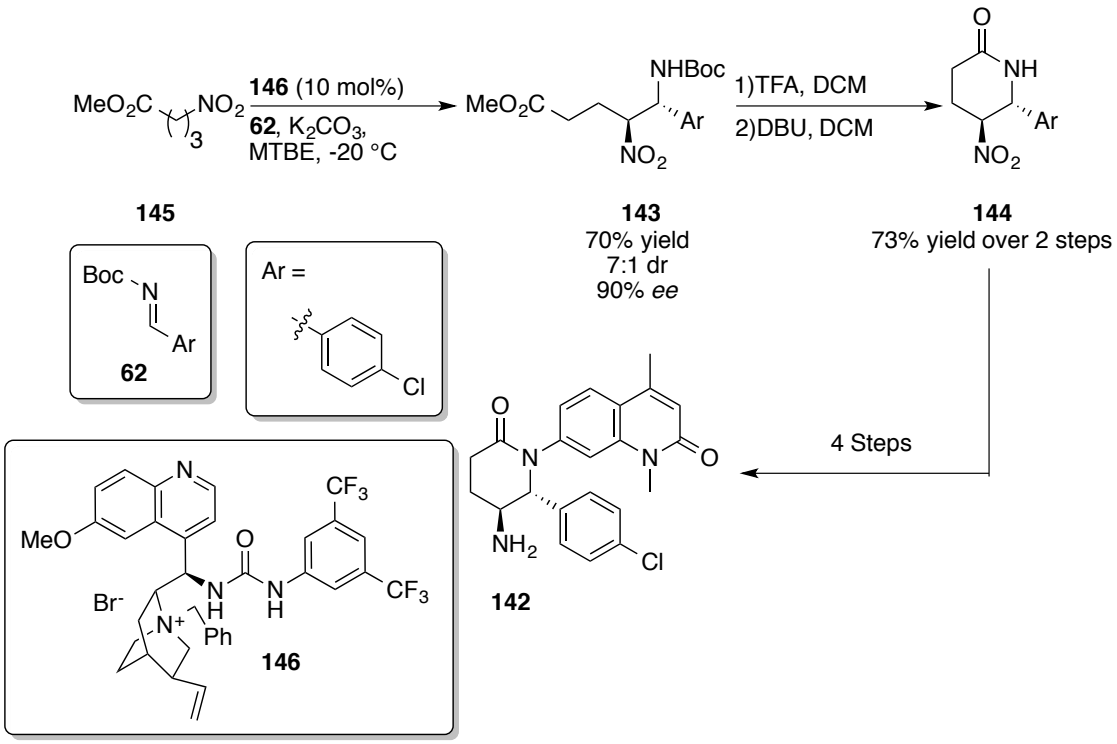
Scheme 34: Synthesis of piperidones **134** by a three-component nitro-Mannich reaction.

This same methodology was then extensively developed by Dixon *et al.* to synthesise heavily decorated 5-nitropiperidin-2-ones by a nitro-Mannich/lactamisation cascade (Scheme 35).[59] The nitro-Mannich/lactamisation cascade was used to great success in their seminal syntheses of both (-)-Nakadomarin A[60] and Manzamine A.[61]



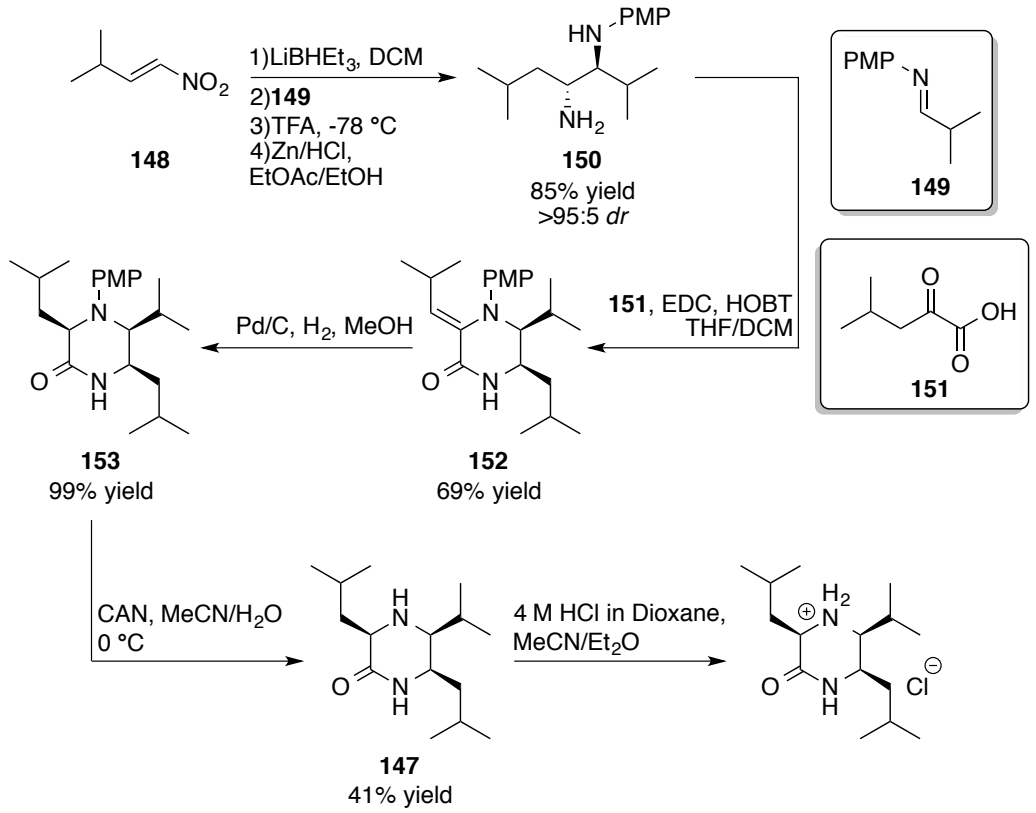
Scheme 35: Synthesis of complex piperidines using cyclic imine **140**.

Later Dixon *et al*. used a similar lactamisation strategy to construct enantioenriched piperidones **142** as the first BRD7/9 bromodomain inhibitors. This strategy involved a phase-transfer catalyzed nitro-Mannich reaction to give nitroamine **143** in a high yield and enantioselectivity, followed by deprotection/cyclisation to give the piperidone **144** in a good yield (Scheme 36).[62]



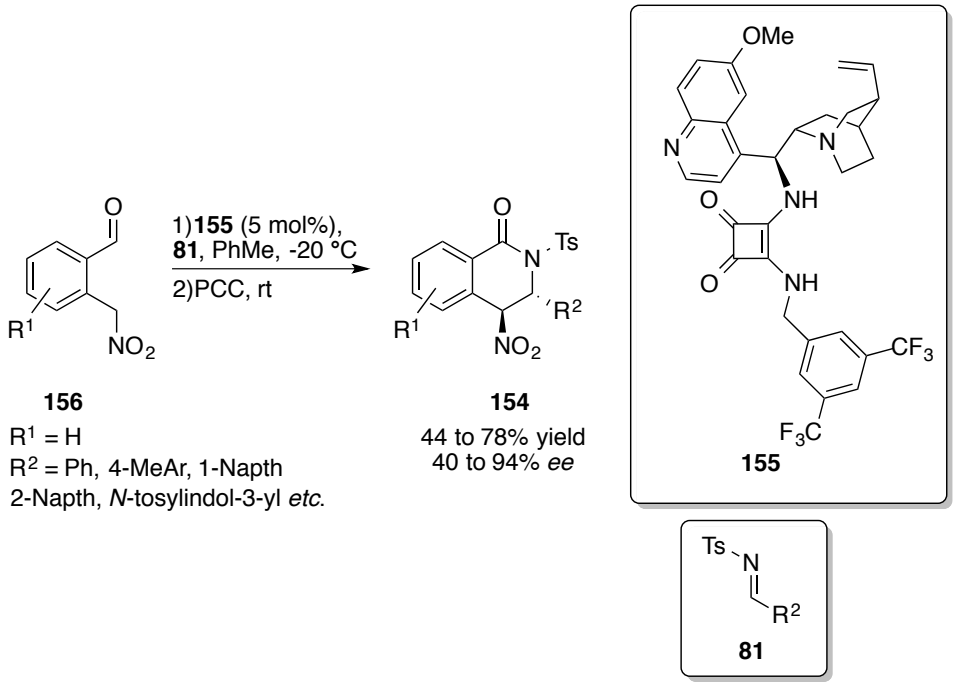
Scheme 36: Synthesis of piperidones **142** as bromodomain inhibitors.

The synthesis of ketopiperazines has also been described by using a nitro-Mannich reaction combined with an amide formation, similar to the lactamisation strategies described above. This strategy was developed as part of Anderson *et al*.'s attempt to synthesise the reported structure of Piperazirum **147** (Scheme 37).[63]



Scheme 37: Nitro-Mannich approach to ketopiperazines through a total synthesis of Piperazirum **147**.

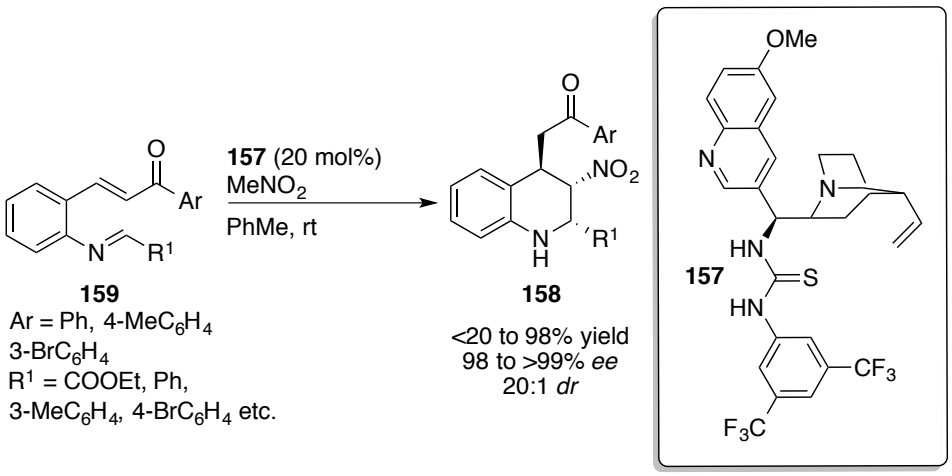
An organocatalytic synthesis of dihydroisoquinolines **154** *via* a one-pot nitro-Mannich-hemiaminalisation-oxidation sequence was described by Enders *et al*. using squaramide **155**. The isolated yields were relatively good and high enantioselectivites could be achieved.[64] While not a true nitro-Mannich/lactamisation sequence, this one-pot hemiaminalisation-oxidation procedure does constitute a formal lactamisation (Scheme 38).



Scheme 38: One-pot nitro-Mannich-Henry-hemiaminalisation-oxidation sequence.

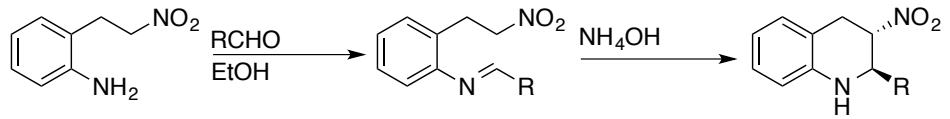
1.9 Intramolecular Nitro-Mannich Approach to Tetrahydroquinolines

There have been few reports of a formal intramolecular conjugate addition nitro-Mannich reaction. However Xu *et al*. have described the Michael addition/nitro-Mannich reaction using nitromethane as a nucleophile in the presence of organocatalyst **157**. This proceeded to give good enantioselectivity, albeit with very long reaction times of 4 to 7 days (Scheme 39).[65] They assigned the relative and absolute stereochemistry of tetrahydroquinoline **158** by X-ray crystal analysis.



Scheme 39: Xu's organocatalytic Michael addition/nitro-mannich reaction.

A one pot imine formation and racemic nitro-Mannich cyclisation has been reported;[66] this proceeds in the presence of a basic additive to give the *trans*-tetrahydroquinoline **160** *via* an intramolecular nitro-Mannich reaction. The method also suffered from relatively long reaction times (Scheme 40). The relative stereochemistry was assigned by analysis of the vicinal coupling constants.



161 **162** **160**

R = Ph, *p*-CF_3Ar, *m*-ClAr, *o*-ClAr, Cy, CO_2Et *etc*.

65 to 93% yield, when R = CO_2Et, 70% conv. 60:40 to >95:5 *dr*

Scheme 40: Intramolecular nitro-Mannich reaction

Both reports detail intramolecular nitro-Mannich reactions to tetrahydroquinolines but gave different stereochemical outcomes. The nitro-Mannich reaction (Scheme 40) gave *trans* whilst the Michael addition/nitro-Mannich reaction (Scheme 39) gave *cis*; this variation was attributed to the different reaction conditions. Xu *et al*. have used a catalyst; the reaction was thought to proceed by kinetic control whilst Anderson *et al*. have forgone a catalyst and used an unselective thermal reaction and under acid/base conditions so the reaction is under thermodynamic control. The *cis* selectivity of the Michael/nitro-Mannich cascade has been rationalised by a tethered Zimmerman-Traxler transition state (Figure 8), which accounts for this stereoselectivity.

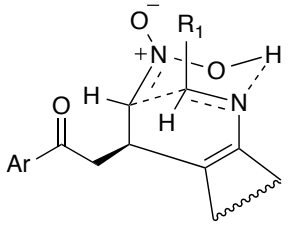
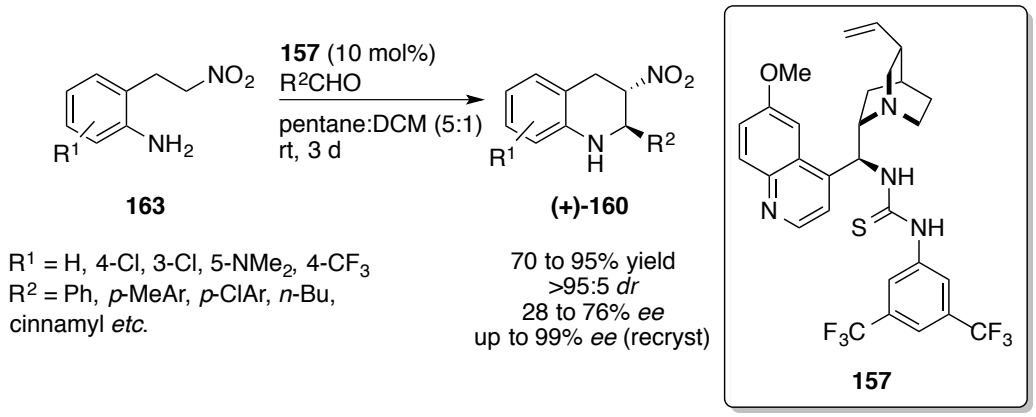


Figure 8: Proposed transition state for the organocatalytic cascade reported by Xu *et al*.

Maity *et al*. described the same intramolecular nitro-Mannich reaction as Anderson *et al*., but controlled the absolute stereochemistry with the same Cinchona catalyst **157** as Zhou *et al*. had used for their Michael/nitro-Mannich cascade. When the intramolecular nitro-Mannich reaction was performed with **157** the *trans*-tetrahydroquinoline **160** was made in high yields and diastereoselectivity (Scheme 41). Unfortunately

enantioselectivity was poor, but the *ee* could be improved by recrystallisation.[67]



Scheme 41: Organocatalysed intramolecular nitro-Mannich reaction.

The report assigned the relative and absolute stereochemistry by X-ray crystal analysis; they rationalized the control of the absolute stereochemistry by suggesting the plausible transition state **164** (Figure 9). It describes the catalyst binding with the substrate in a bifunctional mode with the nitronate attacking from the *Si* face. The report did not discuss their reasoning for the high diastereoselection and the observation that their reaction provided the opposite relative stereochemistry to Xu *et al*. even though they use the same catalyst and propose the same mechanism.

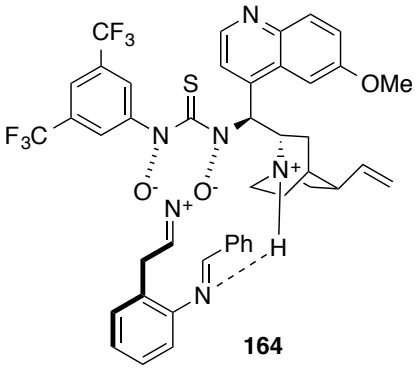
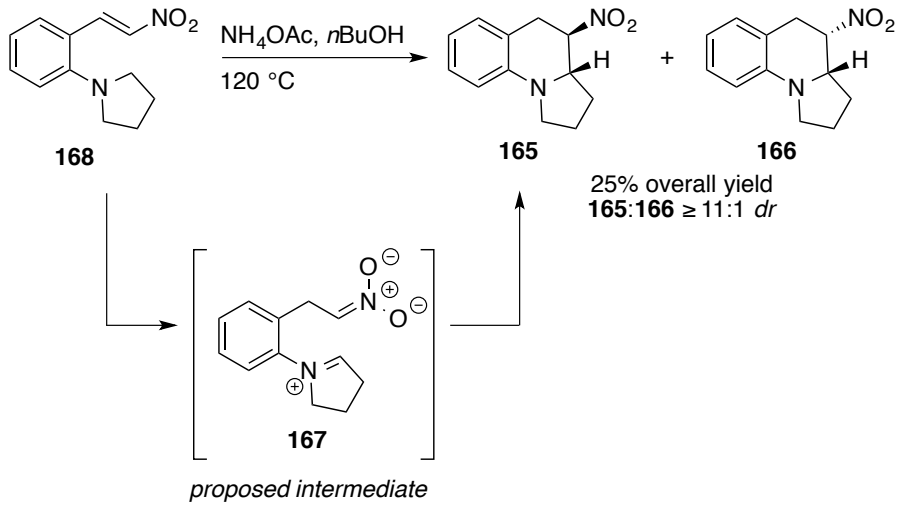


Figure 9: Suggested transition state accounting for the absolute stereochemistry.

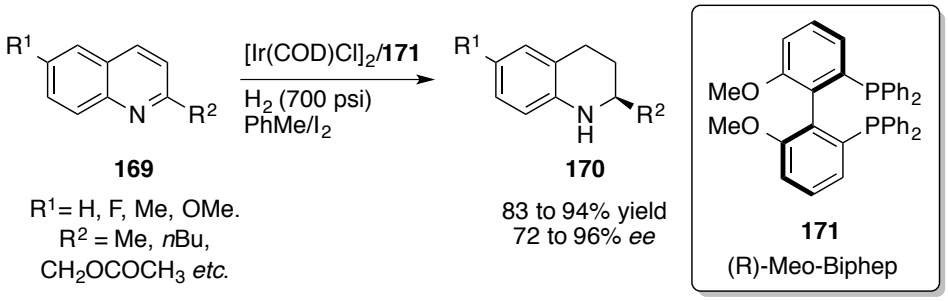
An intramolecular nitro-Mannich reaction to give tetrahydroquinolines **165** and **166** was described by Jordis *et al*. during their investigation into the "T-reaction". This reaction involves an intramolecular 1,5-hydride shift to generate a nitronate and iminium *in situ,* intermediate **167** then undergoes an intramolecular nitro-Mannich reaction (Scheme 42). This reaction was poor yielding (25%) and gave a mixture of diastereomers (≥ 11:1 *dr*), but it represents a particularly interesting redox-neutral generation of both the active nitronate and iminium *in situ*.[68]



Scheme 42: Redox-neutral nitro-Mannich reaction.

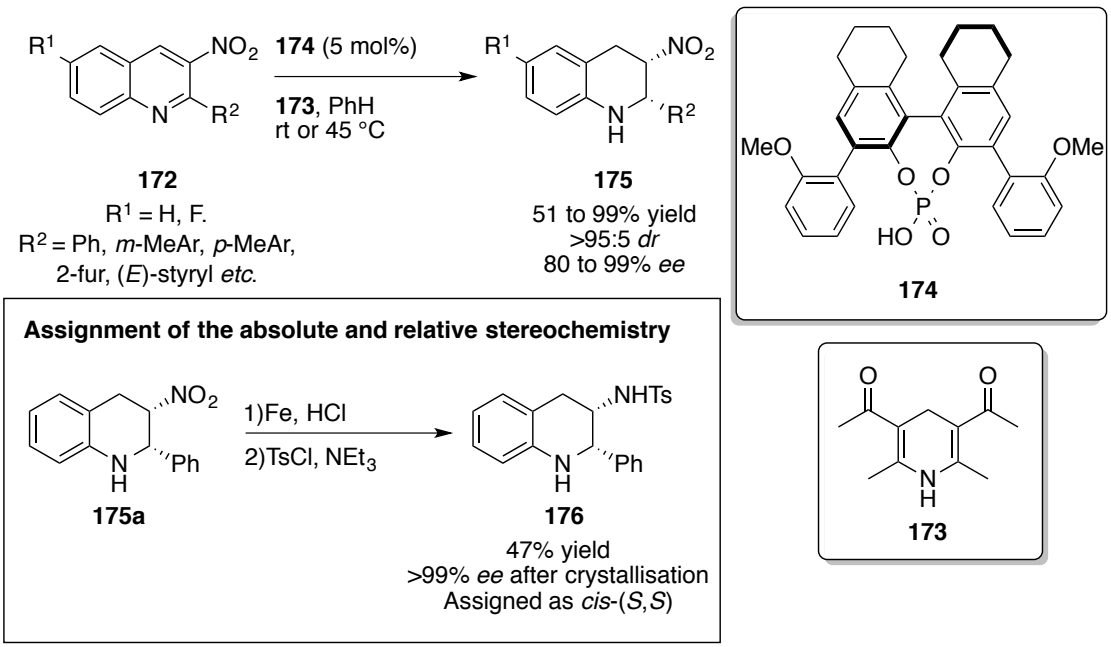
1.10 Other stereoselective approaches to the synthesis of tetrahydroquinolines

Densely functionalised tetrahydroquinolines are frequently synthesised by either hydrogenation of quinolines or by *de novo* construction of the ring.[69] There have been extensive studies into the asymmetric hydrogenation of quinolines. These reports usually use a chiral phosphine ligand and either an iridium or rhodium catalyst. Zhou *et al*. described the highly enantioselective hydrogenation of quinolines **169** to the tetrahydroquinoline **170** (Scheme 43), in high yields but the substrate scope was relatively limited and the high pressures of hydrogen gas limit its operational simplicity/safety. This methodology has been applied to the synthesis of various tetrahydroquinoline natural products.[70]



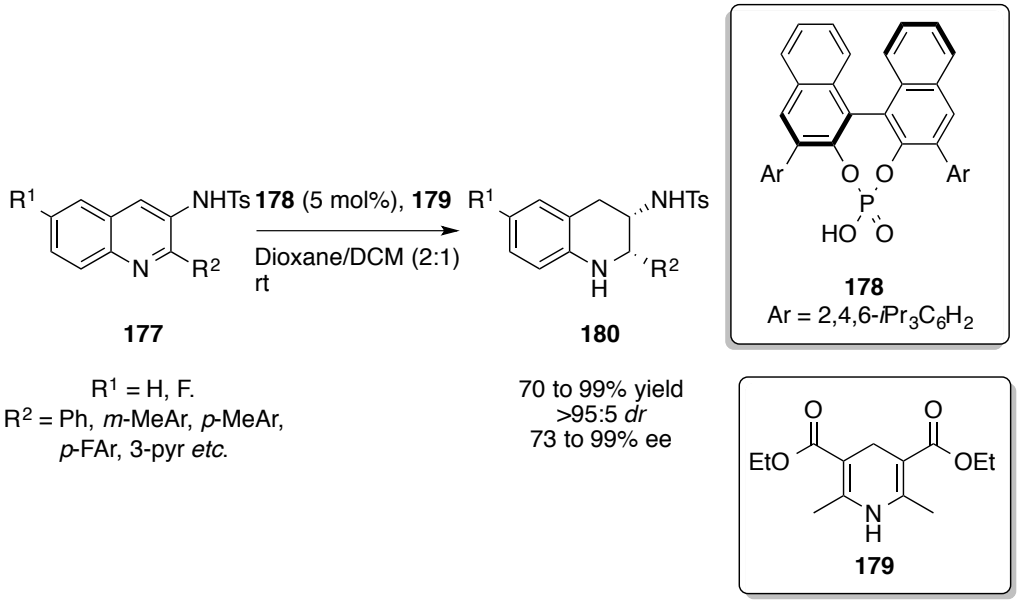
Scheme 44: Asymmetric iridium catalyzed hydrogenation of quinolones **169**.

Further investigation by Zhou *et al*. into the asymmetric hydrogenation of quinolines led to the discovery that 3-nitroquinolines **172** are not easily hydrogenated using transition metal catalysts. Instead using Hantszch ester **173** and chiral phosphoric acid **174** they can be effectively hydrogenated to the *cis*-tetrahydroquinoline **175** in good yields and enantioselectivities, as one diastereomer (Scheme 44).[71] They converted the nitro group to an amine with Fe/HCl and then tosylated the amine to get the *N*-tosyl derivative **176**, this was used to assign the relative and absolute stereochemistry by X-ray crystallography and anomalous dispersion techniques.



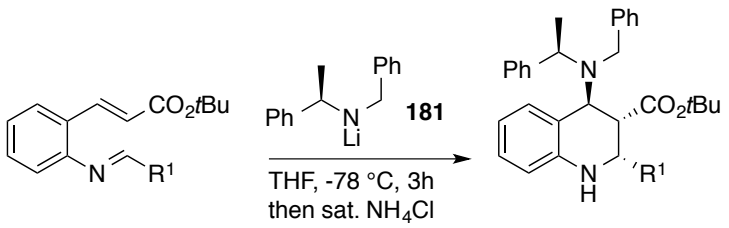
Scheme 44: Organocatalytic transfer hydrogenation of 3-nitroquinolines **172**.

They then investigated a similar transformation; the asymmetric reduction of 3-*N*-tosylquinolines **177** using a similar catalyst **178** and hydride source **179**. This also produced high enantio and diastereoselectivity, with a similar substrate scope (Scheme 45).[72]



Scheme 45: Organocatalytic transfer-hydrogenation of 3-*N*-tosylaminoquinolines **177**.

Tandem cyclisation reactions have garnered high popularity in recent years, as this is a particularly effective method of creating the tetrahydroquinoline core (or other heterocycles) with multiple stereocenters, in one-pot. Davies *et al*. triggered a Michael/Mannich cascade by the addition of the chiral ammonia equivalent **181** to α,β-unsaturated ester/imine **182**. This gave high diastereoselectivies and yields, but the substrate scope was limited to only a few aryl/heteroaryl groups (Scheme 46).[73]



182

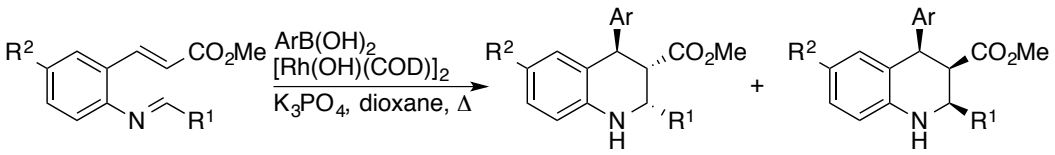
R^1 = *p*-CF_3Ar, *p*-OMeAr, 2-fur, *o*-MeAr

183

72 to 82% yield
>95:5 *dr*
>98% *ee*

Scheme 46: Tandem synthesis of densely functionalised tetrahydroquinolines **183** by an asymmetric Michael addition/Mannich cascade.

Use of an arylboronic acid and a rhodium (I) catalyst has also been shown by Youn *et al.* to trigger a Michael/Mannich cascade approach to the synthesis of densely functionalised tetrahydroquinolines. This procedure allows the efficient construction of densely functionalised tetrahydroquinolines **184** and **185** with good to high yields and good diastereoselectivity. (Scheme 47).[74] They suggested a Zimmerman-Traxler transition state with a Rh^I-enolate intermediate to account for the observed diastereoselection.



186

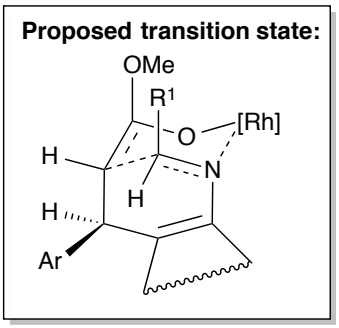
Ar = Ph, *p*-OMeAr, 2-Naphth, *p*-FAr *etc.*
R^1 = CO_2Et, *p*-OMeAr, *p*-NO_2Ar, *o*-BrAr, cinnamyl *etc.*
R^2 = H, Me

184

185

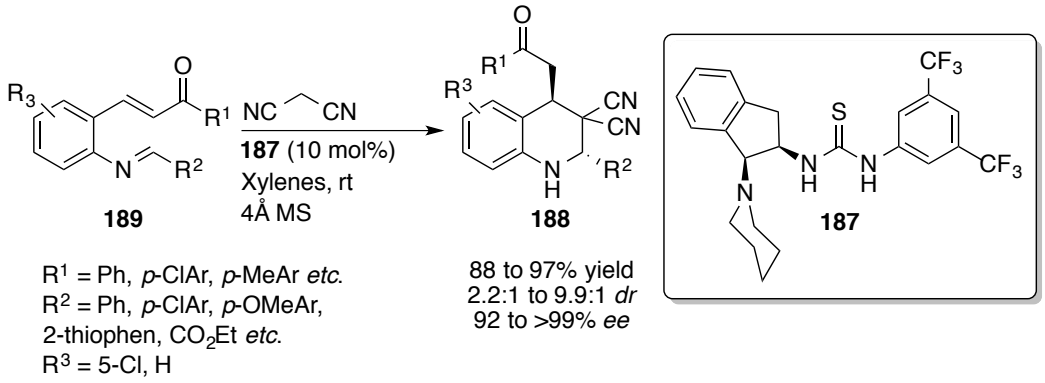
33 to 86% yield
50:50 to >95:5 dr

Proposed transition state:



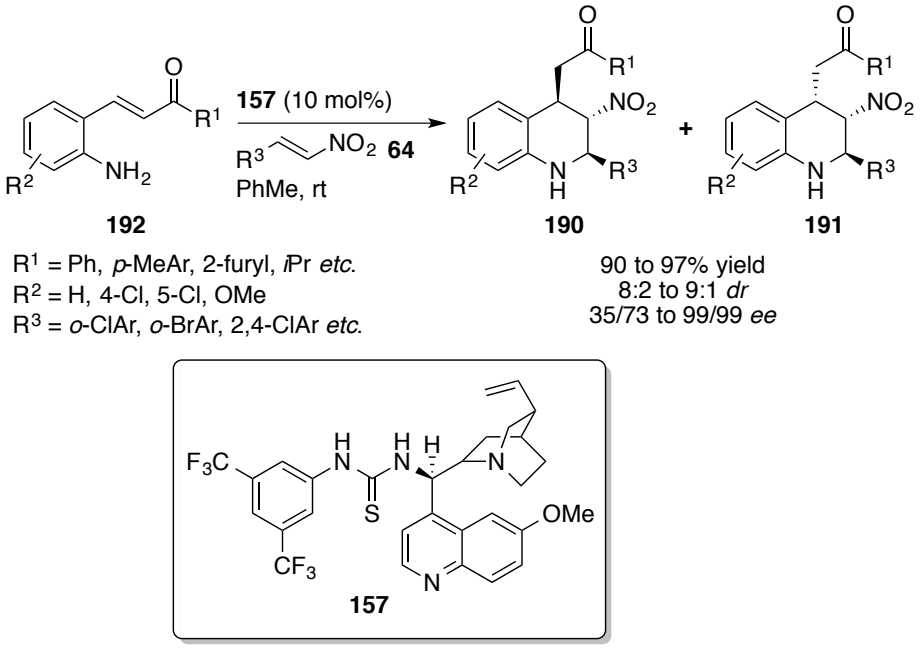
Scheme 47: Rhodium catalyzed conjugate addition/Mannich cyclisation.

Most other examples rely on organocatalysis as the means to trigger these cascade reactions. Wang *et al*. used a bifunctional chiral thiourea catalyst **187** and malonitrile as a nucleophile to form the desired tetrahydroquinoline **188**. A series of control experiments were performed that indicated that the reaction proceeded by a Mannich-Michael sequence (Scheme 48).[75]



Scheme 48: Synthesis of tetrahydroquinolines **188** using malonitrile as a double nucleophile.

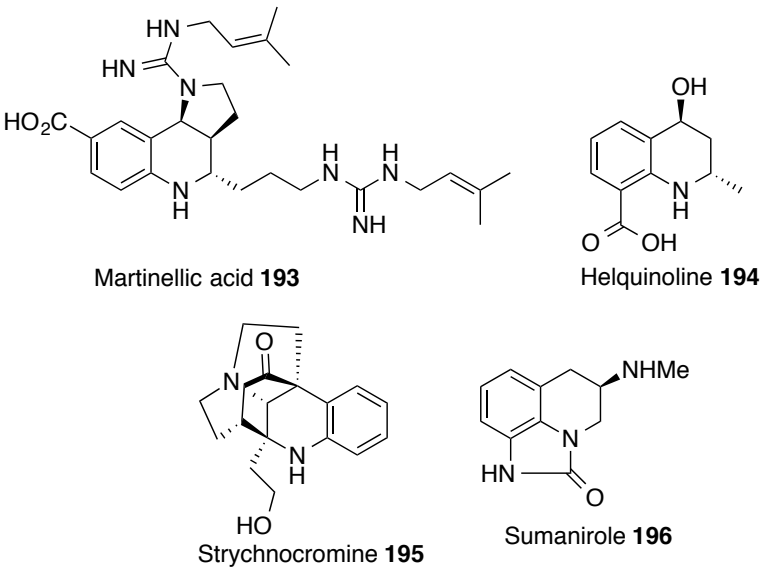
Another cascade approach to trisubstituted-tetrahydroquinolines was described by Xu *et al*. that is complementary to their Michael/nitro-Mannich cascade. In this report they describe a Michael/Michael cascade that gave the *trans*,*trans*-tetrahydroquinoline **190** and *trans*,*cis*-tetrahydroquinoline **191** in good yields and stereoselectivity. An interesting limitation of this methodology is that it usually only works when R^3 is an *ortho*-substituted aryl group (Scheme 49).[76]



Scheme 49: Cascade approach to *trans*,*trans*-tetrahydroquinoline.

1.11 Importance of Tetrahydroquinolines

Tetrahydroquinolines are found in numerous natural products and pharmaceuticals. Martinellic acid **193** has antimicrobial activity and has a micro molar binding affinity to G-protein coupled receptors (GPCR) and so has been the focus of a few total syntheses.[77] Another tetrahydroquinoline based antibiotic is Helquinoline **194** (Figure 10).[78] There are some reports of 3-aminotetrahydroquinolines being present in natural products and bioactive molecules, too. Strychnocromine **195** is an alkaloid isolated from the bark of *Strychnos gossweileri* by Quentin-Leclerq *et al*.; the same group revised the structure by analysis of the X-ray structure and 2D-NMR spectroscopy and showed that it contains the caged 3-aminotetrahydroquinoline motif.[79] The D_2 agonist Sumarindole **196** contains a 3-aminotetrahydroquinoline motif and was originally developed for the treatment of Parkinson's disease.[80]



Martinellic acid **193**

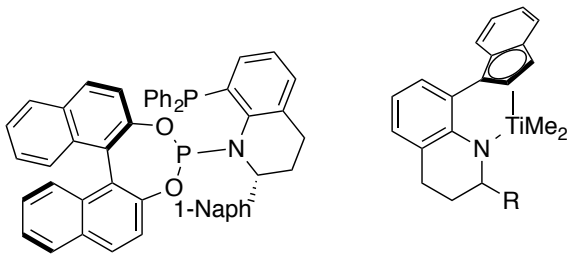
Helquinoline **194**

Strychnocromine **195**

Sumanirole **196**

Figure 10: Examples of biologically active tetrahydroquinolines.

In addition to their biological uses, some chiral tetrahydroquinolines have been investigated as ligands for asymmetric synthesis (Figure 11). The phosphoramidite ligand Quinaphos **197** has been used as a ligand for the Rh-catalysed hydrogenation of acrylates and aminoacrylates.[81] The tetrahydroquinoline based titanium complex **198** has found an application as an ethylene/1-octene copolymerization catalyst.[82]



Quinaphos **197** **198**

R = H, Me, *n*Pr, *t*Bu, $(CH_2)_6O$*t*Bu

Figure 11: Chiral ligands with the tetrahydroquinoline motif.

As the motif is frequently encountered in various areas of chemistry, efficient and stereocontrolled synthesis of tetrahydroquinolines continues to be of high importance.[69]

2.0 Proposed Research

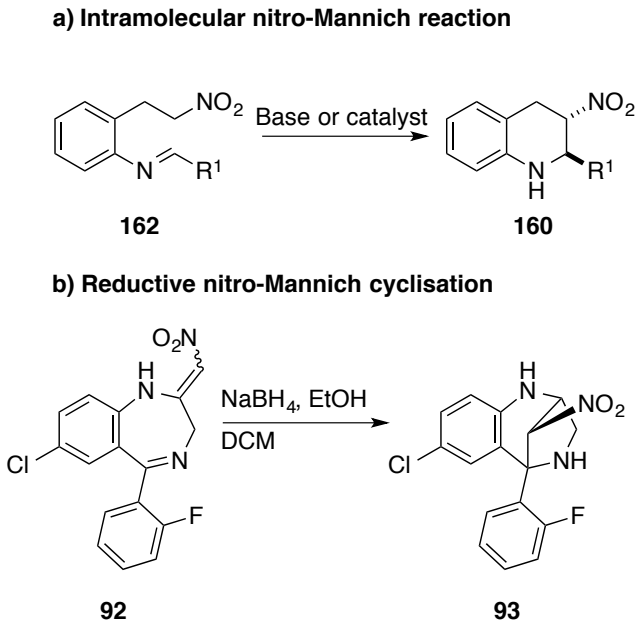
It has been shown that the organocatalytic reductive nitro-Mannich reaction can give 1,2-nitroamines in high enantio and diastereoselectivity; these can subsequently be isolated as their trifluoroacetamides in high yields.

It has also been shown that the intramolecular nitro-Mannich reaction can provide tetrahydroquinolines in an expedient fashion with good yields and diastereoselectivity. Despite these two reactions being successful, the use of the organocatalytic reductive nitro-Mannich reaction has never been applied in the stereoselective synthesis of *N*-Heterocycles. The combination of the reductive nitro-Mannich reaction and intramolecular nitro-Mannich reaction would address the following points:

- The synthesis of nitrostyrenes tethered to an imine remains unaddressed in the literature.
- Reports of a tandem reductive intramolecular nitro-Mannich reaction remain scarce.
- Intramolecular cyclisation provides a green alternative to the Buchwald-Hartwig approach that involves functional group manipulations, protecting groups and the use of expensive and finite palladium.
- The tandem reaction might be trigged by the addition of other nucleophiles, either organocatalytically or by a transition metal catalyst.

2.1 Precedent for an Intramolecular Conjugate Addition Nitro-Mannich Reaction

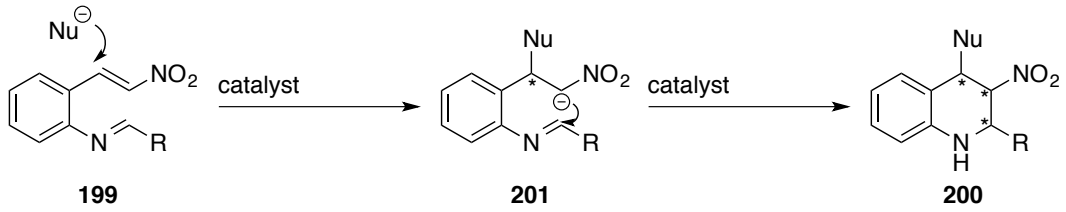
There have been limited reports of intramolecular nitro-Mannich reactions. These have been limited to standard nitro-Mannich reactions[66] or unexpected cyclisations of specific substrates in the literature (Scheme 50).[45]



Scheme 50: Literature precedent for an intramolecular nitro-Mannich reaction.[45, 66]

2.3 Chosen Strategy

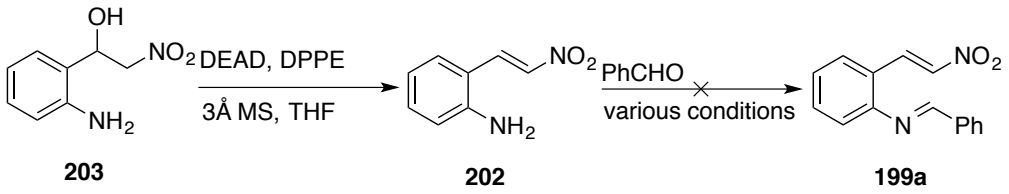
We hoped that by merging the conjugate addition nitro-Mannich reaction with a tethered nitrostyrene **199** onto an imine, a tandem cyclisation might occur to give the tetrahydroquinoline **200** in high yields (Scheme 51). This strategy would remove the need for functional group manipulations and protecting groups that are currently necessary to get stereo-defined tetrahydroquinolines.



Scheme 51: Cascade cyclisation to give tetrahydroquinoline **200** from nitrostyrene **199**.

Synthesis of the tethered nitrostyrene **199** has previously been shown to be difficult.[75] The most logical disconnection, an imine formation from the parent nitroamine (Scheme 52), has been shown to be unsuccessful within the group. Wang *et al*. have previously mentioned that they were

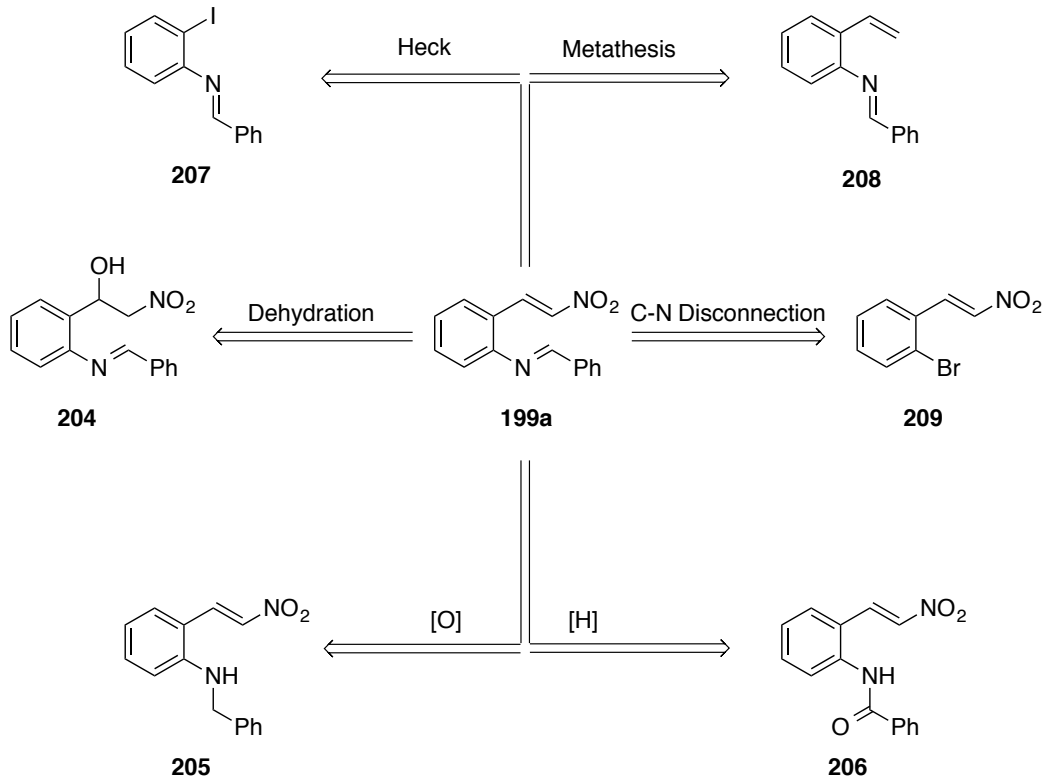
unsuccessful in synthesizing 2-aminonitrostyrene **202**. During our investigations the synthesis of 2-aminonitrostyrene was found to be possible but isolation was difficult as it would polymerise on silica gel, but it could be made *in situ* and then used as a reactant (Scheme 52).



203 **202** **199a**

Scheme 52: Imine formation between 2-aminonitrostyrene and benzaldehyde.

A strategy to bypass the nitrostyrene until the final stages was hypothesised, as the direct imine formation between **202** and an aldehyde proved troublesome. The synthesis of nitrostyrene **199a** could be done by 4 alternative strategies (Scheme 53): dehydration of nitroalcohol **204**, a Pd catalyzed C-N bond formation, oxidation of benzylic amine **205**[83] or reduction of amide **206**.[84] Two other potential disconnections are a Heck or metathesis reaction between **207** or **208** and nitroethylene; these two disconnections are not possible, however, as it has been shown that nitroethylene is unreactive in both the Heck reaction[85] and olefin metathesis.[86]



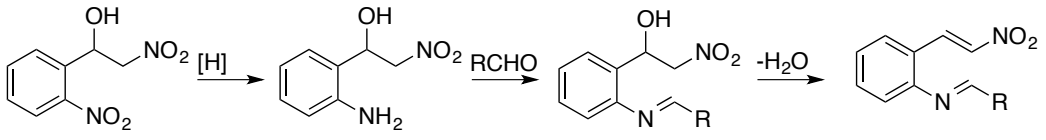
Scheme 53: Potential disconnection routes to nitrostyrene **199a**.

With this in mind, our focus was turned towards the dehydration strategy using nitroalcohol **204** as the most promising disconnection to nitrostyrene **199**.

3.0 Results and Discussion

3.1 Synthesis of Amine 203

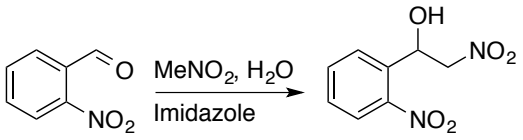
It was thought that if the nitrostyrene was bypassed until the final step, synthesis of tethered nitrostyrene **199** would occur in a facile manner *via* imine **204** (Scheme 54) through the use of a dehydration reaction. The imine **204** could be made from the corresponding aryl amine **203**, which is made by selective hydrogenation of the nitroalcohol **210** using Pd/C.



210 **203** **204** **199**

Scheme 54: Imine formation/dehydration route to nitrostyrene **199**.

Nitroalcohol **210** could be made by a simple Henry reaction between 2-nitrobenzaldehyde and nitromethane in water using imidazole as a catalyst. The desired nitroalcohol **210** could be isolated pure without the use of column chromatography in quantitative yield (Scheme 55).[87]



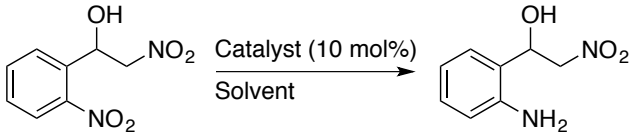
210
100% yield

Scheme 55: Synthesis of nitroalcohol **210**.

Hydrogenation of the nitroalcohol **210** in EtOH for 6 hours gave the aryl amine **203** in 58% yield. When the reaction was scaled up to more than 5 g, the yield was severely diminished to 9%. A solvent screen (Table 1) showed that a 1:1 mixture of ethyl acetate and DCM was optimal, allowing for a scale up to about 10 g with no discernable decrease in yield. Further optimisation came by addition of equimolar Pearlman's catalyst; this led to an improvement in the yield of up to 77% (entry 5).[88] In order to try to increase the yield even more, Pt/C was used as the

catalyst, as it has been noted to reduce aryl nitro groups faster than Pd/C. Unfortunately 10 mol% Pt/C gave a complex mixture.

Table 1: Aryl nitro hydrogenation screen.



210 **203**

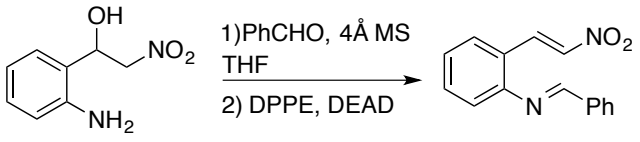
Entry	Catalyst	Solvent	Yield (%)
1	Pd/C	EtOH	58%
2	Pd/C	EtOH	9 %[a]
3	Pd/C	DCM	46 %[a]
4	Pd/C	DCM/EtOAc (1:1)	50 %[a]
5	Pd/C & $Pd(OH)_2$/C	DCM/EtOAc (1:1)	77%[a]
6	Pt/C	EtOAc	-

[a]Reaction scale >5 g.

When nitro reductions are performed, sometimes the newly formed amine can poison the catalyst by irreversible binding to the metal center. Methods to recover lost catalytic activity include the *in situ* Boc protection or protonation of the amine. As our product **203** has the free hydroxyl and the amine, that could poison the catalyst, the addition of acid additives (dilute HCl or AcOH) was investigated. This modification only led to a retro-Henry degradation of the starting material.

3.2 Imine formation and elimination

Elimination of the alcohol to form a nitrostyrene by a Mitsunobu reaction had been investigated within the group by Joshua Barham;[89] this suffered from a very low isolated yield (8%) and the separation from the triphenylphosphine and triphenylphosphine oxide residues was laborious (Scheme 56). It was observed that the imine formation was very slow in this reaction and that heating the reaction mixture or using a desiccant such as molecular sieves led to decomposition of the starting material.

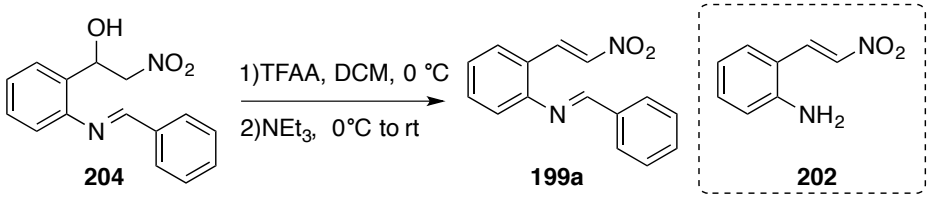


203 **199a**

20% conversion by ^{1}H NMR
after 24 h
8% isolated yield

Scheme 56: Previous dehydration of nitroalcohol **203** to nitrostyrene **199a**.

Other methods for dehydration were attempted, DCC/CuCl-mediated elimination as reported by Seebach *et al*.[90] failed to provide any conversion to the nitrostyrene. Trialling BOP with NEt_3 as a potential dehydrating agent gave a complex mixture. Thankfully addition of TFAA then triethylamine to **204** afforded nitrostyrene **199a** in 20-63 % yield (Scheme 57), the variable yields being due to the hydrolysis of **199a** to **202**.

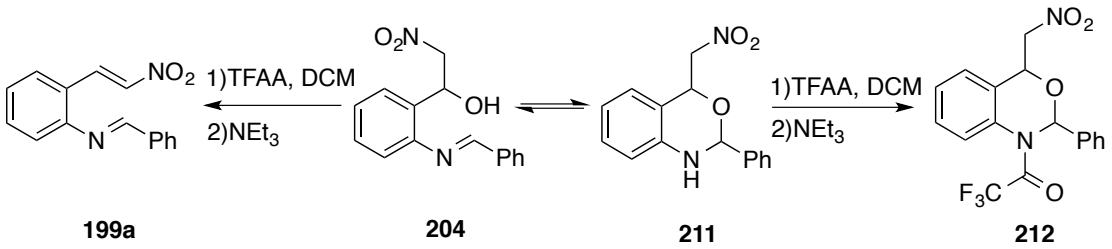


204 **199a** **202**

20 to 63% yield

Scheme 57: One pot imine formation-alcohol elimination to nitrostyrene-imine **199a**.

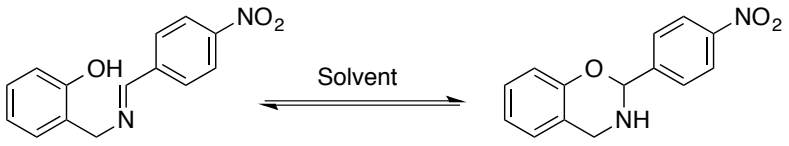
Conversion to the nitrostyrene **199a** was limited by the equilibrium between the open nitro-alcohol **204** and the hemi-aminal **211**.[91] Both **204** and **211** are able to react with trifluoroacetic anhydride (Scheme 58), leading to the undesired by product **212** and nitrostyrene **199a**. The hemiaminal **211** could be observed by ^{1}H NMR of the crude reaction mixture and after addition of TFAA/NEt_3 a quartet signal was visible at ~160 ppm in the ^{13}C NMR of the crude reaction mixture, indicative of *N*-trifluoroacetamide **212**.



199a **204** **211** **212**

Scheme 58: Formation of nitrostyrene and competitive hemiaminal formation.

It was thought that the solvent might affect the ratio of alcohol **204** and hemiaminal **211**. Previously Smith *et al*. had shown that the polarity of the solvent can have an effect on the ratio between the Schiff base and the hemiaminal.[92] The reasoning behind this phenomenon is the more polar the solvent, the stronger the hydrogen bonding between the solvent and the free hydroxyl, hence making a free hydroxyl group thermodynamically more favorable (Scheme 59).



213

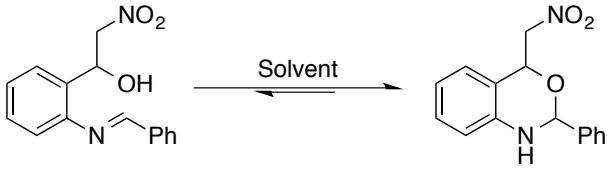
CH_3CN = 40% **214**
C_2D_5OD = 19% **214**
DMSO = 0-3% **214**

214

Scheme 59: Comparison by ^1H NMR of solvent on Schiff base/hemiaminal ratio as reported by Smith *et al*.

A solvent screen indicated that most solvents favoured the hemiaminal **211** except for THF and nitromethane (Table 2). By the previous study DMSO would have been a very good choice for our reaction, but DMSO/TFAA/NEt_3 is a modified Swern oxidation procedure and so wasn't used.

Table 2: Solvent effect on hemiaminal vs. imine formation

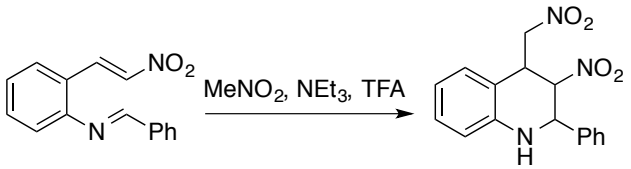


204 **211**

Solvent	204:211[a]
DCM	40:60
$MeNO_2$	70:30
PhCHO (neat)	35:65
MeCN	40:60
MeOH	45:55
THF	50:50

[a]Ratio estimated by ^{1}H NMR of the crude reaction mixture.

Nitromethane was particularly effective, providing good conversion to the desired imine **204**. Standard trifluoroacetylation and elimination of the alcohol to nitrostyrene **199a** with $MeNO_2$ as a solvent did not provide the desired imine-nitrostyrene **199a** but another product was visible in the crude ^{1}H NMR; this is proposed to be tetrahydroquinoline **215**. This undesired product could be made by the nitromethane solvent reacting with the nitrostyrene product **199a** (Scheme 60). Isolation of **215** was attempted, but prior to column chromatography the product decomposed within hours when stored at -15 °C.

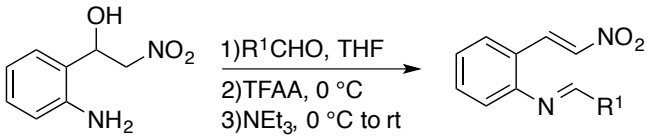


199a **215**

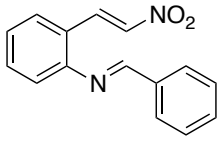
Scheme 60: Proposed undesired product after reaction performed in $MeNO_2$.

With this in mind, THF was selected as the reaction solvent, which led to an increase in yield of **199a** to 67 %. Molecular sieves were also omitted to stop decomposition of the starting material. Increasing the equivalents of TFAA from 1 to 2 suppressed the formation of 2-aminonitrostyrene **202** made by imine hydrolysis, increasing the reliability of the yields from 20-63% to consistently 67%. With optimal conditions found, the substrate scope was investigated (Table 3). It was found that while the reaction gave good yields when R^1 = Phenyl, it shut down when other functional groups were used.

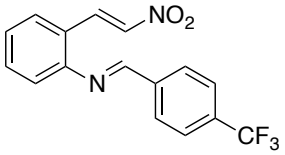
Table 3: Synthesis of nitrostyrenes **199**.



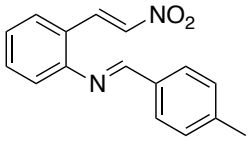
203 **199**



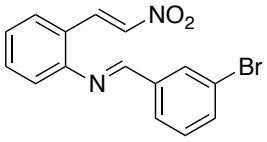
199a, 67% yield



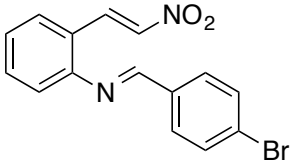
199b, 28% yield



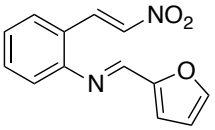
199c, 27% yield



199d, 32% yield



199e, 11% yield

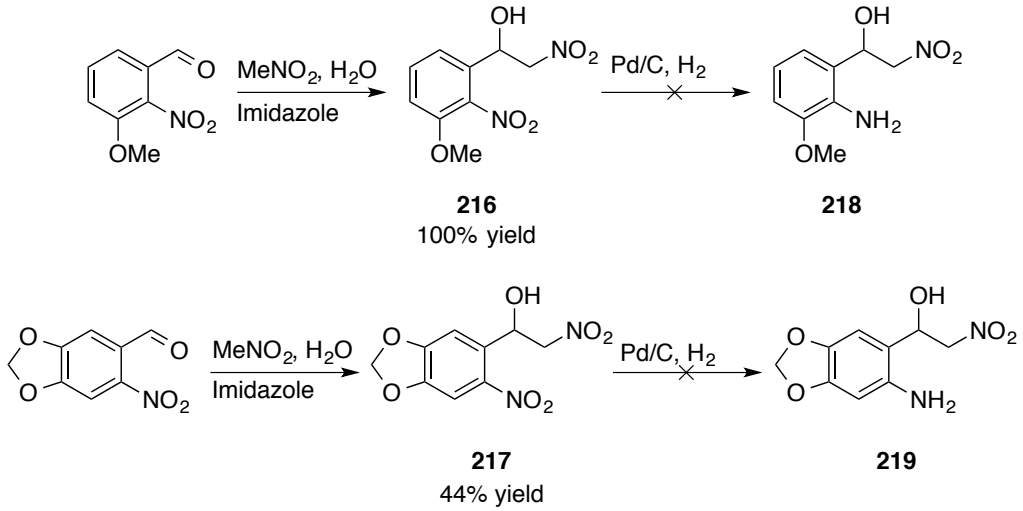


199f, 26% yield

The poor conversions can be attributed to two effects: the poor nucleophilicity of aryl amine **203** means that the imine formation is very slow and the starting material decomposes before complete conversion to the imine, hence the low yields when R^1 = electron rich. The equilibrium between imine **204** and hemiaminal **211** is also affected by the electronics of the R group; when R^1 = electron deficient the imine is more electrophilic and so the equilibrium moves towards the hemiaminal. The effect of *para*-substituents on the ratio of hydroxyl and hemiaminal has

previously been discussed by McDonnell *et al*. showing a preference for cyclisation when R^1 = electron withdrawing.[91]

In order to find more suitable substrates, the synthesis of various functionalised aryl amines was attempted by the previous strategy of hydrogenation of the nitroalcohol. Nitroalcohols **216** and **217** were made by the previously reported Henry reaction, but when hydrogenation was performed using Pd/C and H_2 none of the desired product was formed (Scheme 61), only a complex mixture.

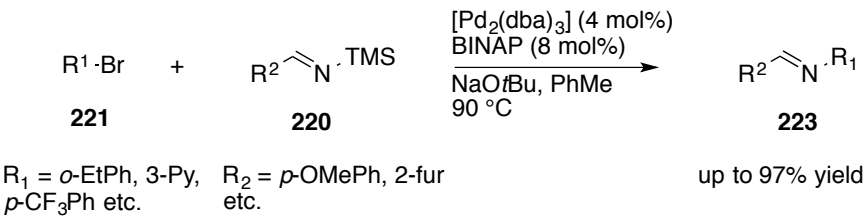


Scheme 61: Attempted synthesis of amines **218** and **219**.

At this juncture it became evident that this disconnection involving imine intermediate **204** is not the ideal retrosynthesis. Further work was done to find a second-generation synthesis of nitrostyrene-imine **199**.

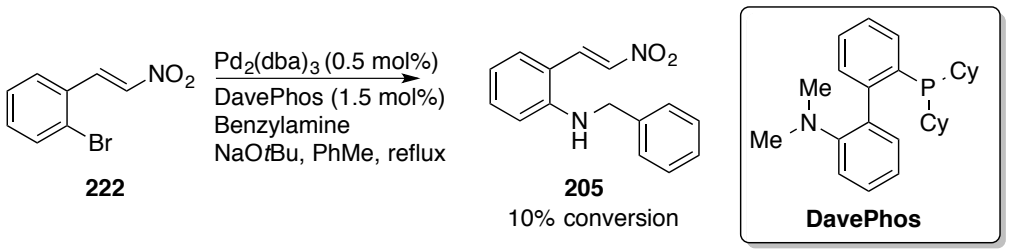
3.3 Investigation into a 2nd Generation Synthesis of Nitrostyrene 199

As previously mentioned, other potential disconnections could involve a Buchwald-Hartwig type imine formation. This was investigated; both a direct imine coupling and a standard amine coupling were investigated. Barluenga *et al*. had described the direct coupling between *N*-silyl imine **220** and aryl bromides **221** (Scheme 62), and so application to *ortho*-bromo nitrostyrene **222** seemed a valid extension.[93]



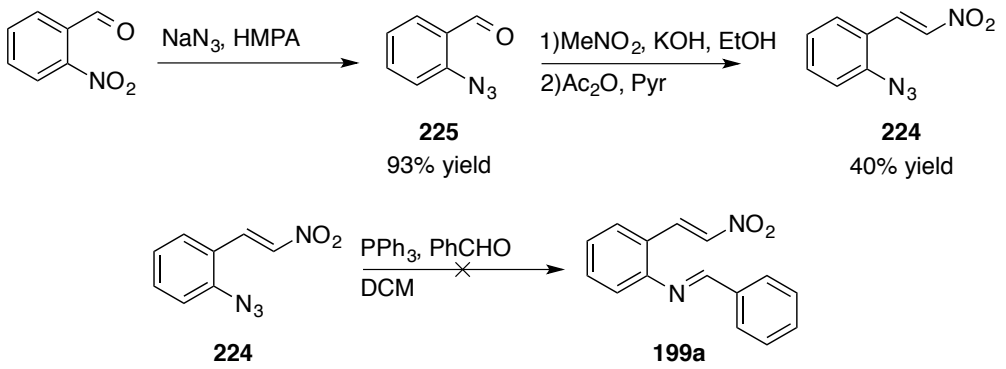
Scheme 62: Previous report by Barluenga *et al*.

When the same conditions were applied to *ortho*-bromonitrostyrene **222** no product was formed, only recovered starting material. A Buchwald-Hartwig coupling was then attempted, as this might be more successful. Using standard coupling conditions, only 10% conversion to **205** was observed by ^{1}H NMR (Scheme 63). With this in mind other disconnections were investigated.



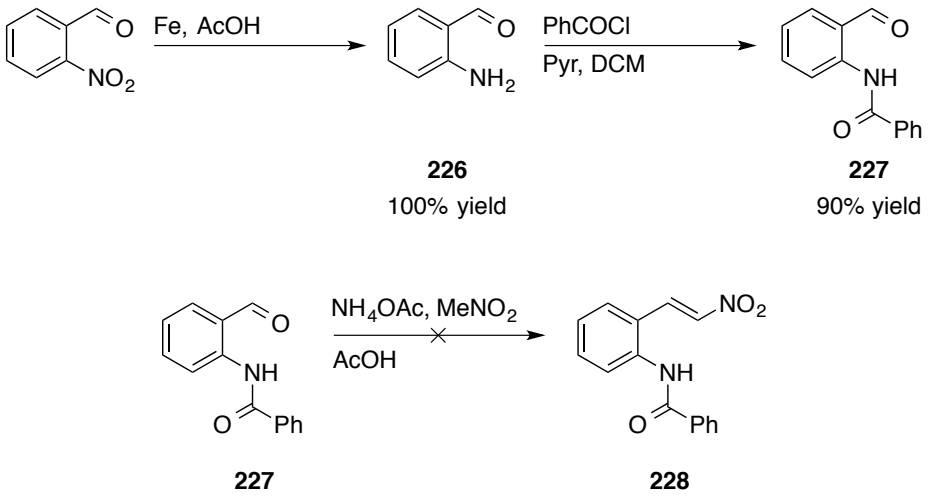
Scheme 63: Buchwald-Hartwig coupling.

An aza-Wittig approach was then investigated. When 2-azidonitrostyrene **224** was reacted with benzaldehyde and triphenylphosphine, imine **199a** was not formed (Scheme 64).[94]



Scheme 64: Attempted aza-Wittig reaction between aryl azide **224** and benzaldehyde.

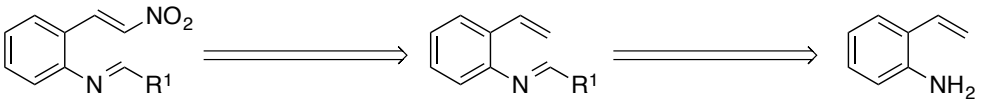
The reduction of the amide to the imine looked like a promising route on paper. Synthesis of the starting material was not possible, though. Reduction of 2-nitrobenzaldehyde to the 2-aminobenzaldehyde **226,** then conversion to the *N*-Benzoyl amine **227** was high yielding and operationally simple but attempts to form the nitrostyrene **228** were unsuccessful (Scheme 65).[95]



Scheme 65: Attempted synthesis of *N*-Benoyzlnitrostyrene **228**.

3.4 Late-Stage Nitration Strategy

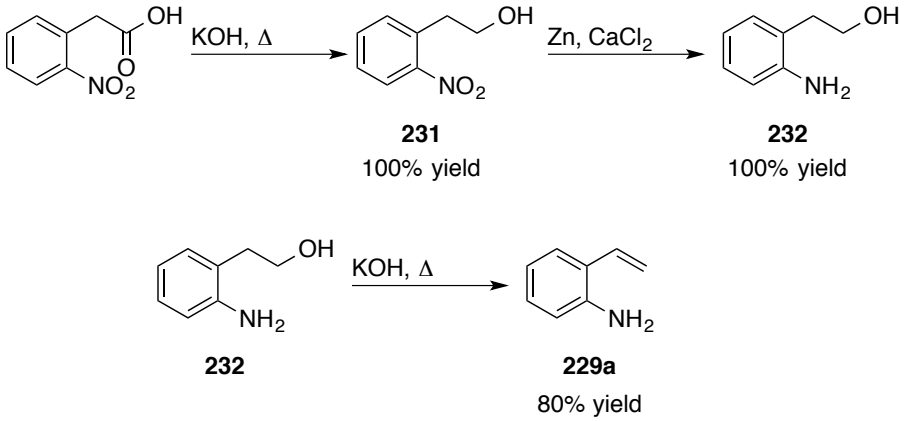
An alternative method of synthesising nitroalkenes is the nitration of a vinyl group, usually performed by CAN, HNO_2 or $C(NO_2)_4$.[96] A drawback of these methods is their functional group incompatibility or safety issues. A recent report by Maiti *et al*. demonstrated a mild nitration method with a broad substrate scope, which could be a promising avenue for the synthesis of nitrostyrene **199**.[97, 98] This methodology was therefore investigated; the route would involve imine formation between 2-aminostyrene **229a** and an aldehyde, then nitration of the pendant vinyl group to the nitrostyrene (Scheme 66).



199 **230** **229a**

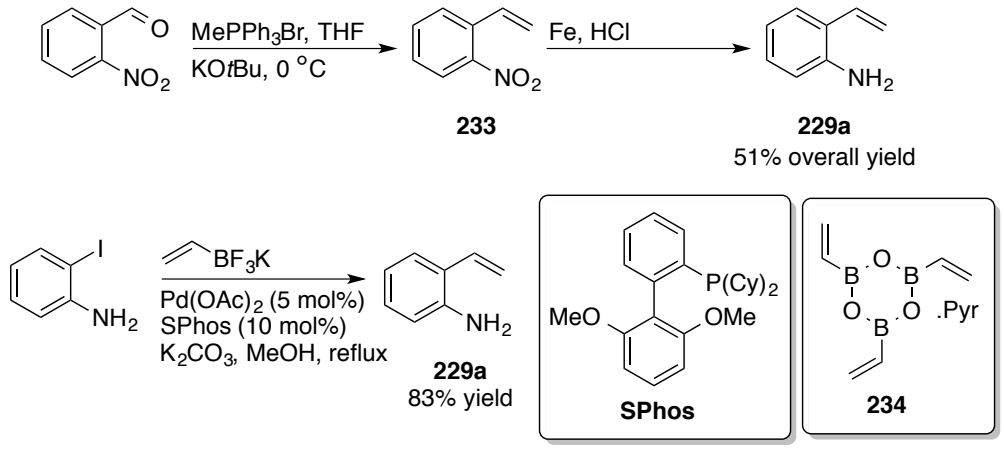
Scheme 66: Potential disconnection to the nitrostyrene.

The preparation of 2-vinylaniline **228a** required the reduction of 2-nitrophenylacetic acid to the alcohol **231**,[99] reduction of the nitro group to the amine **232**[100] and then dehydration using KOH (Scheme 67).[101] This process was highly scalable and hence very useful.[102]



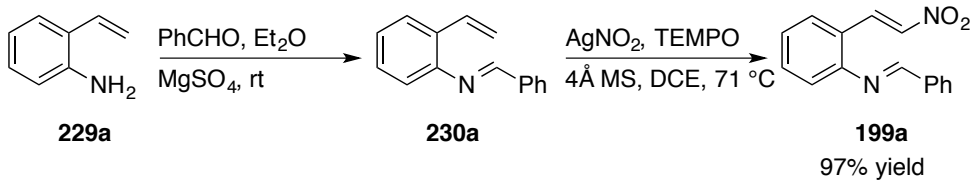
Scheme 67: Synthesis of 2-vinylaniline **229a**.

Other methods reported and investigated include Wittig olefination of 2-nitrobenzadehyde to 2-nitrostyrene **233** and reduction of the nitro group to amine **229a**[103] or Suzuki vinylation of 2-iodoaniline using either O'Shea's reagent **234**[104] or potassium vinyltrifluoroborate (Scheme 68).[105, 106] These methods were difficult to scale up; the Wittig olefination involved large columns to try and separate large quantities of triphenylphosphine oxide residues, while the Suzuki coupling only worked well if the scale was under 1g.



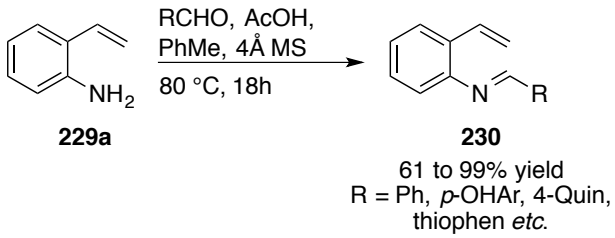
Scheme 68: Alternative routes investigated to give 2-vinylaniline **229a**.

Imine formation between 2-aminostyrene **229a** and benzaldehyde proceeded with complete conversion after 48 hours at room temperature, following the procedure developed by Martinez *et al*.[107] After imine formation, radical nitration using the conditions described by Maiti *et al*. gave the desired nitrostyrene **199a** in a yield of 97% (Scheme 69).



Scheme 69: Synthesis of imine **230a** and then nitration to nitrostyrene **199a**.

Pleasingly imine formation and nitration from 2-aminostyrene **229** was high yielding with various aryl aldehydes or ethyl glyoxylate (Table 6). The reaction solvent was changed from Et_2O to DCE/AcOH and the reaction was heated at reflux as this helped decrease the reaction times for electron rich aldehydes.[108] Use of DCE also meant that imine formation and nitration could be performed in a one-pot telescoped fashion too, with no detriment to the yield. During this investigation Buchwald *et al*. described the synthesis of these imines with a more rapid procedure that cut the reaction time down to up to 18 h (Scheme 70).[105]



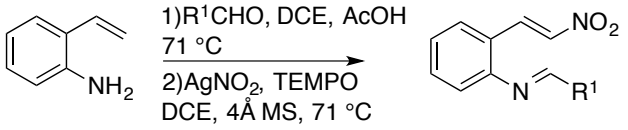
229a **230**

61 to 99% yield
R = Ph, *p*-OHAr, 4-Quin,
thiophen *etc*.

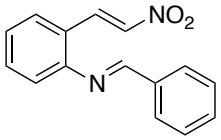
Scheme 70: Improved imine formation reported by Buchwald et al.

When the imine formation and nitration procedure was repeated using *n*-hexanal, pivaldehyde or cyclohexanecarboxaldehyde, only complex mixtures were obtained. It is thought that the reaction conditions are too vigorous for unstable alkyl imines. Nevertheless this approach gives an entry point into previously unobtainable analogues.

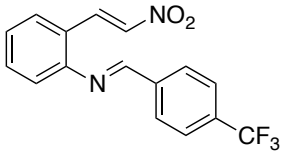
Table 6: Nitrostyrene-imine substrates.



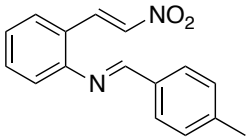
229a **199**



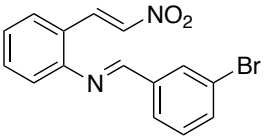
199a, 97% yield



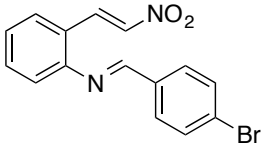
199b, 95% yield



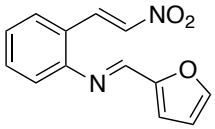
199c, 94% yield



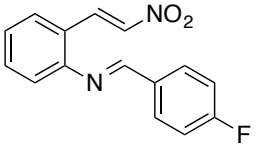
199d, 95% yield



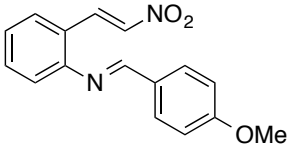
199e, 44% yield



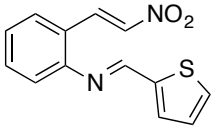
199f, 88% yield



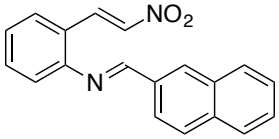
199g, 94% yield



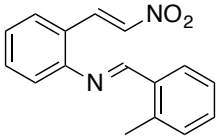
199h, 51% yield



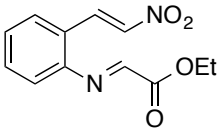
199i, 86% yield



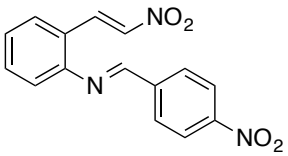
199j, 73% yield



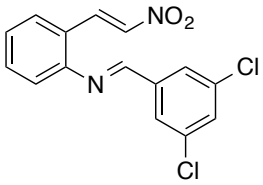
199k, 51% yield



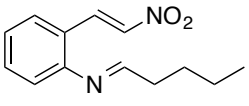
199l, 15% yield



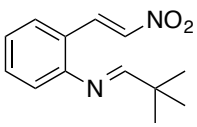
199m, 82% yield



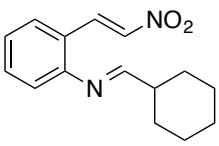
199n, 42% yield



199o, 0% yield

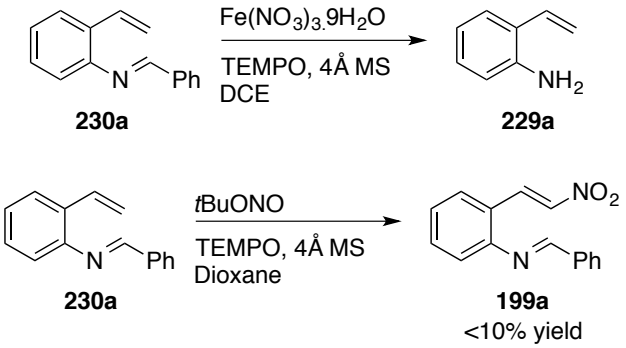


199p, 0% yield



199q, 0% yield

In order to increase the atom economy and decrease cost of this transformation, other nitrating agents were used that had been reported by Maiti *et al*. These included $Fe(NO_3)_3.9H_2O$[98] and *t*BuONO.[109] Unfortunately in our hands these were not useful. Nitration using $Fe(NO_3)_3.9H_2O$ gave the parent 2-aminostyrene back by imine hydrolysis and *t*BuONO gave poor yields <10% (scheme 71).

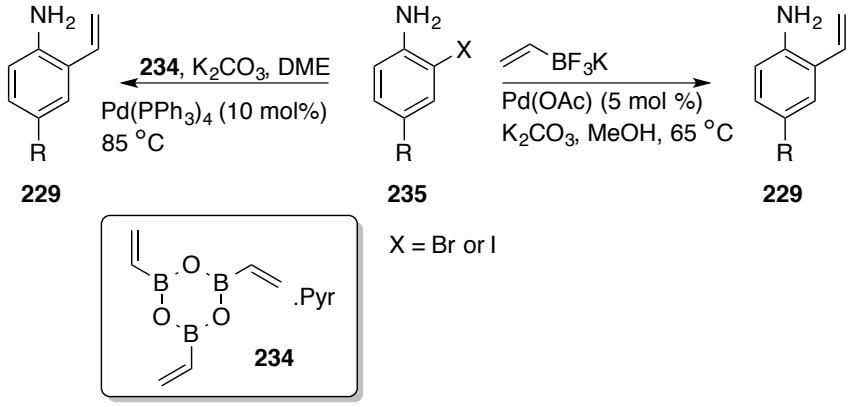


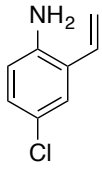
Scheme 71: Investigation into the use of cheaper nitrating agents.

3.5 Expanded Aminostyrene and Nitrostyrene Synthesis

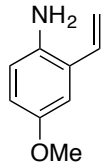
Various 2-aminostyrenes **228** could be synthesised by Suzuki coupling chemistry, using either potassium vinyltrifluoroborate or O'Shea's reagent **234** as the vinylboronic acid surrogate. These gave the desired 2-vinylanilines in goods yields (Table 7). While some of these products have been made by Stille couplings, Suzuki couplings were preferred due to the poor atom economy and the presence of tributyltin residues that are difficult to separate by column chromatography when performing a Stille reaction.

Table 7: Synthesis of 2-vinylanilines by Suzuki coupling.

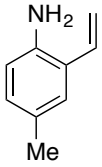




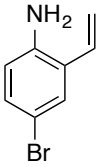
229b, 55% yield



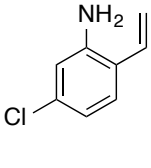
229c, 44% yield



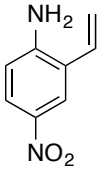
229d, 41% yield



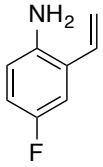
229e, 49% yield



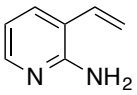
229f, 47% yield



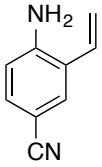
229g, 17% yield



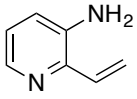
229h, 71% yield



229i, 60% yield



229j, 49% yield

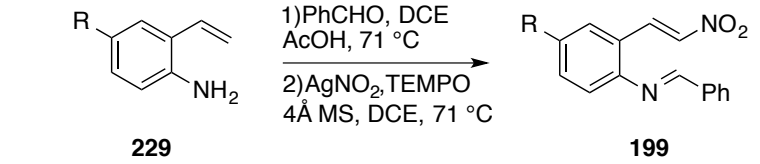


229k, 82% yield

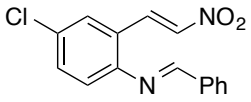
The 2-aminostyrenes **229** could then be condensed with benzaldehyde and nitrated to give the desired nitrostyrenes **199r**, **199s**, **199t** and **199u** (Table 8)**.** When electron deficient 2-aminostyrenes **199w, 199x**, **199y**

and **199z** were used, no desired product was formed, as polymerisation occurred or the starting material remained unreacted.

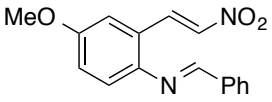
Table 8: Use of aminostyrenes **229** to form nitrostyrenes **199**.



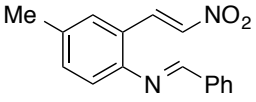
229 **199**



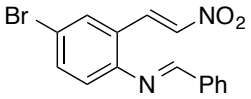
199r, 93% yield



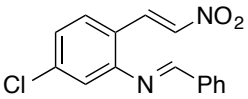
199s, 28% yield



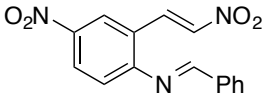
199t, 63% yield



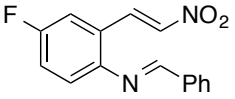
199u, 43% yield



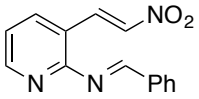
199v, 0% yield (polymer)



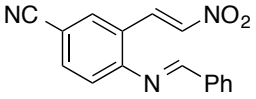
199w, 0% yield (RSM)



199x, 0% yield (polymer)



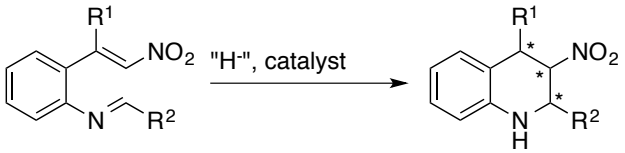
199y, 0% yield (polymer)



199z, 0% yield (RSM)

3.6 Synthesis of α–Substituted Tethered Nitrostyrenes

It was thought that if there was a substituent on the α-position of the nitrostyrene then the tandem cyclisation may give tetrahydroquinoline **236** with three stereocenters in high yields and stereoselectivity (Scheme 72).

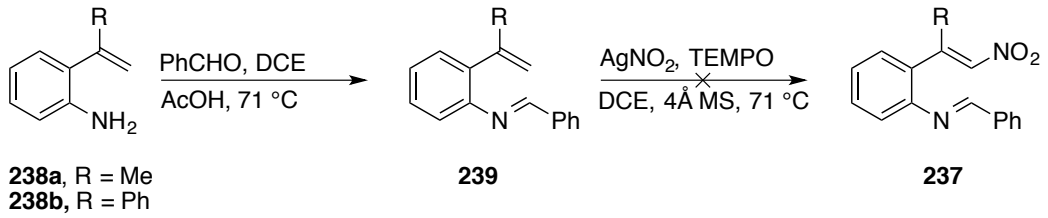


237 **236**

R^1 = Me, Ar *etc.*
R^2 = Ar, COOEt

Scheme 72: Proposed synthesis of densely functionalised tetrahydroquinolines **236**.

The previously described imine formation and nitration procedure was then extended to try to make 1,1-disubstituted nitrostyrenes **237** from the corresponding anilines **238**. Imine formation with 2-aminostyrene **238a** and **238b** gave the desired imine **239**, albeit in longer reaction times, but when the nitration procedure was then performed, decomposition of the imine intermediate was observed to give an insoluble black tar (Scheme 73).



238a, R = Me
238b, R = Ph

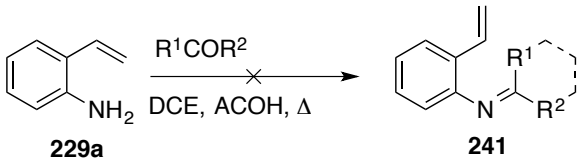
239

237

Scheme 73: Synthesis of 1,1-disubstituted nitrostyrenes **237**.

3.7 Ketimine Synthesis

The synthesis of ketimines **240** was then attempted, as these could be used to make a tetrahydroquinoline with a chiral quaternary center. Direct imine formation between 2-aminostyrene **229** and Acetophenone was unsuccessful. As one issue could be the enolisation of the ketimine intermediate, a ketone without α-protons was investigated too. Unfortunately 2,2,2-trifluoroacetophenone failed to undergo ketimine formation either (Scheme 74). The lack of reactivity may be due to the *ortho*-styrene group, as this deactivates the aniline both electronically and sterically, so it is thought that the amine may not be reactive enough to do a direct imine formation with a ketone.



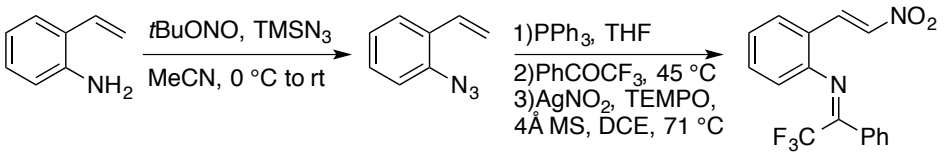
229a

241

R^1COR^2 = $PhCOCH_3$, $PhCOCF_3$, cyclohexanone

Scheme 74: Failed direct ketimine formation using 2-aminostyrene **229a**.

A modified tactic was then investigated, where the aniline **229a** was converted to azide **242** by diazotization. Azide formation using *t*BuONO and $TMSN_3$ gave the 2-azidostyrene in a 90% yield (Scheme 75). Azide **242** successfully condensed with 2,2,2-trifluoroacetophenone by an aza-Wittig reaction and was then nitrated to give nitrostyrene **240a**.[110]



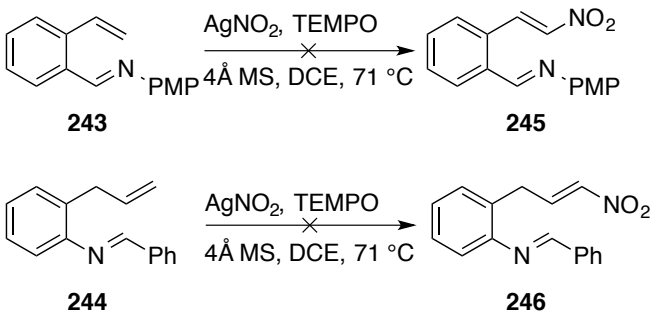
229a | **242** 90% yield | **240a** 45% yield

Scheme 75: Synthesis of ketimine **240a**.

Application of this procedure to benzophenone, acetophenone or cyclohexanone failed to provide the desired ketimine **240**. It is thought that benzophenone is too hindered for the already sterically bulky iminophosphorane intermediate, while acetophenone and cyclohexanone have enolisable protons that can be deprotonated by the basic iminophosphorane intermediate, preventing an aza-Wittig reaction.

3.8 Miscellaneous Nitrostyrene Synthesis

Nitration of imines **243** and **244** were attempted to increase the product diversity (Scheme 76). In each case decomposition of the starting material occurred; when **243** was used all that was observed was the parent aldehyde and *p*-anisidine and when **244** was used complete decomposition was observed.

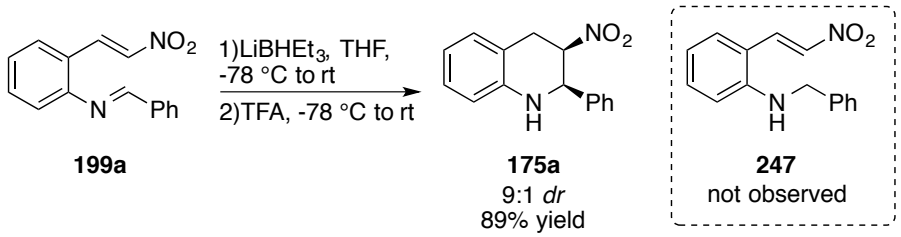


Scheme 76: Attempted nitration of vinyl and allyl imines **243** and **244**.

Allylic and benzylic protons are known to undergo radical type transformations, such as the MnO_2 or CAN mediated oxidations. Decomposition of **244** might be due to a similar type process of radical based allylic/benzylic H-abstraction and then polymerization, decomposition or oxidation. With many tethered nitrostyrenes synthesised and potential analogues exhausted further attention was focused on addition of nucleophiles to these novel sensitive nitrostyrenes and cyclisation studies.

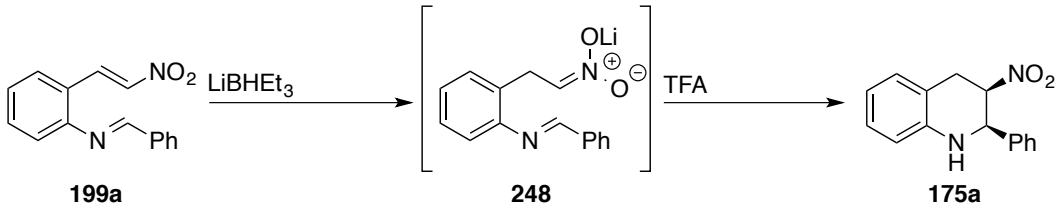
3.9 Intramolecular Nitro-Mannich Reaction - Tandem Cyclisation

Reductive cyclisation of nitrostyrene **199a** using superhydride in THF at -78 °C, then addition of TFA gave solely the tetrahydroquinoline **175a** in an 89% yield and 9:1 *dr*. It is interesting to note that no 1,2-addition product **247** was observed by TLC or ^{1}H NMR of the crude material (Scheme 77).



Scheme 77: Reductive cyclisation cascade using superhydride.

In a manner similar to previous nitro-Mannich reactions, the mechanism is thought to proceed by 1,4-hydride addition to the nitrostyrene **199a** giving the stable lithium nitronate **248**. Upon addition of trifluoroacetic acid, the imine is protonated to the iminium and then the nitronate attacks the iminium to give the racemic tetrahydroquinoline **175a** (Scheme).



Scheme 78: Mechanism of the reductive nitro-Mannich reaction.

3.10 Determination of Relative Stereochemistry

The relative stereochemistry was assigned by ^{1}H NMR based on the coupling constants between H_a and H_b. The major diastereomer **175a** had a $J_{Ha\text{-}Hb}$ = 4.1 Hz while the minor diastereomer **160a** has a $J_{Ha\text{-}Hb}$ = 7.9 Hz. Assuming a chair-like conformation one would expect a *trans* configuration to have a $J_{Ha\text{-}Hb}$ = ~8 Hz and *cis* $J_{Ha\text{-}Hb}$ = ~4 Hz. On this basis, the major diastereomer was assigned as *cis* (Figure 12).[66]

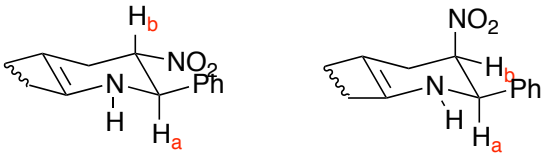


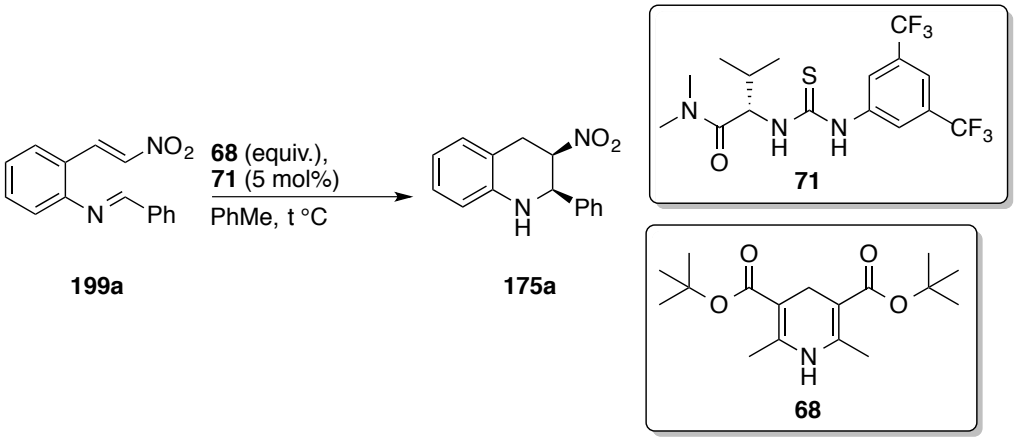
Figure 12: Coupling constants for *cis* and *trans* relative stereochemistry.

The relationship between the relative stereochemistry and the ^{3}J coupling constant had previously been confirmed by Zhou *et al*. in their synthesis of *cis*-2-aryl-3-nitro-tetrahydroquinolines from 2-aryl-3-nitroquinolines.[68] They confirmed this relationship by X-ray crystal analysis of the *N*-tosylated *cis*-3-amino-tetrahydroquinoline that was prepared from the corresponding *cis*-3-nitro-tetrahydroquinoline (Scheme 44).

3.11 Organocatalysis

As a reductive nitro-Mannich reaction was indeed possible using superhydride, an organocatalytic procedure was investigated. An organocatalytic synthesis may provide enantiopure tetrahydroquinolines in an expedient manner without the need for an inert atmosphere. Nitrostyrene **199a** was added to Hantzsch ester **68** as the transfer hydrogenation agent and thiourea **71** was used as the organocatalyst, using the conditions described by Anderson *et al.*[33] It was found that decreasing the number of equivalents of Hantzsch ester **68** led to no loss of conversion, while decreasing the temperature from 25 °C to 0 °C gave an increase in enantioselectivity at the expense of reaction time (Table 9).

Table 9: Investigations into organocatalytic cyclisation.

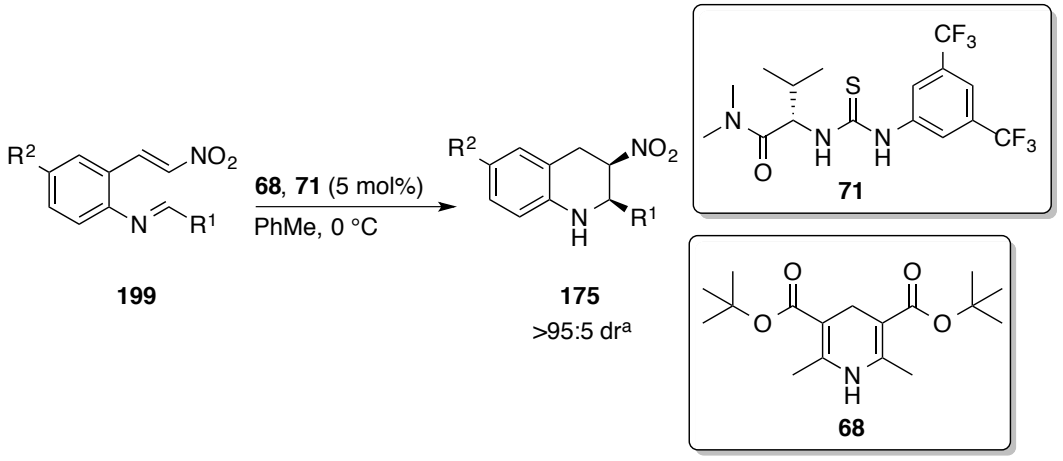


Entry	Temp (°C)	68 (equiv.)	Time (h)	yield[a]	*ee*[b]	*dr*[c]
1	rt	2	12	>95:5	94	>95:5
2	0	2	18	>95:5	97	>95:5
3	0	1	18	>95:5	97	>95:5

[a]Isolated yield, [b]enantiomeric excess determined by chiral phase HPLC, [c]Determined by ^{1}H NMR.

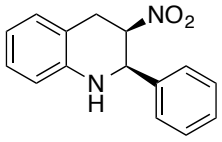
With the organocatalytic procedure giving the desired tetrahydroquinoline in high yields and conversions (with no reduction of the imine), the substrate scope was investigated, using the tethered nitrostyrenes **199** already synthesised (Table 10). This gave in most cases the tetrahydroquinoline in near quantitative yields, as one diastereomer and with high *ee*.

Table 10: Asymmetric tandem reductive nitro-Mannich reaction.

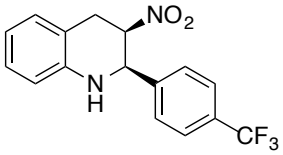


199

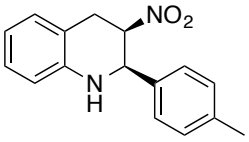
175
>95:5 dr[a]



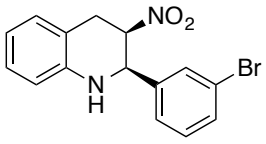
175a, 97% yield, 97% *ee*[b]



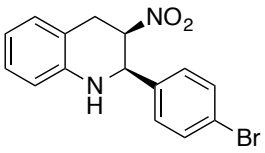
175b, 95% yield, >99% *ee*[b]



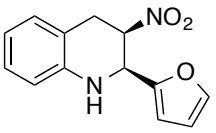
175c, 100% yield. >99% *ee*[b]



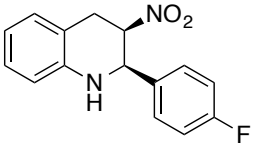
175d, 100% yield, 96% *ee*[b]



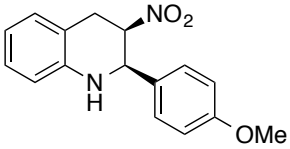
175e, 99% yield, 98% *ee*[b]



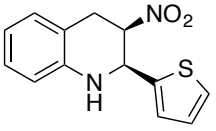
175f, 88% yield, 88% *ee*[b]



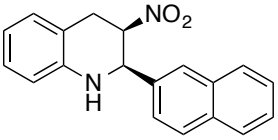
175g, 100% yield, >99% *ee*[b]



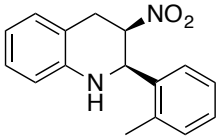
175h, 97% yield, 99% *ee*[b]



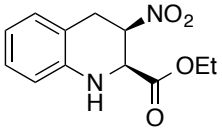
175i, 97% yield, 99% *ee*[b]



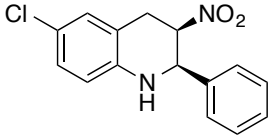
175j, 100% yield, 98% *ee*[b]



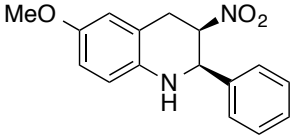
175k, 100% yield, -[c]



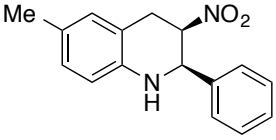
175l, 95% yield, -[d]



175r, 93% yield, 93 *ee*



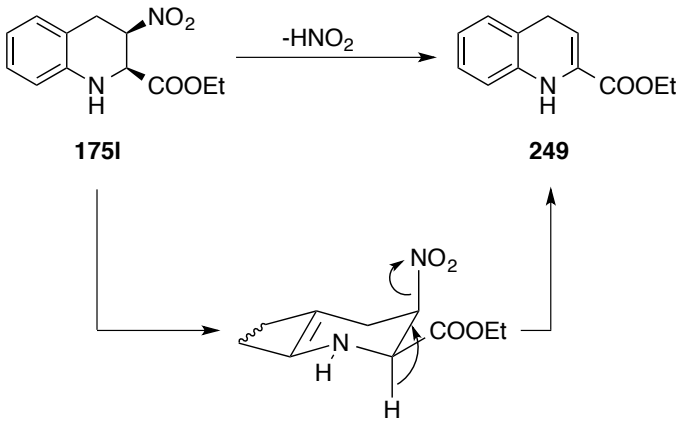
175s, >95% conversion[e]



175t, >95% conversion[e]

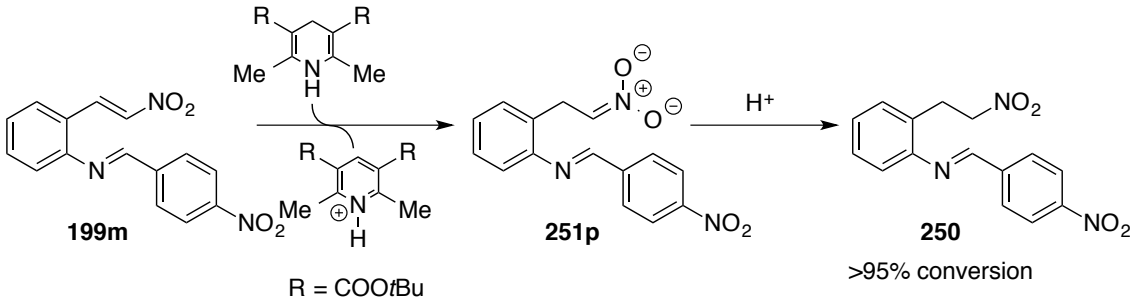
[a]Calculated by ^{1}H NMR, [b]enantiomeric excess determined by chiral phase HPLC, [c]HPLC conditions could not be determined, [d]product unstable to HPLC conditions, [e]Product unstable to column chromatography, conversion determined by ^{1}H NMR.

It was found that if R^1 = COOEt the tetrahydroquinoline product **175l** was unstable at room temperature with the sample slowly turning red, either as a solid or in solution. The observed red colour is thought to be due to the elimination of HNO_2 (Scheme 79). As the compound was unstable at room temperature, this prevented it from being analysed by chiral HPLC.



Scheme 79: Plausible ionic denitration pathway of tetrahydroquinoline **175l**.

When R^1 = *p*-NO_2Ar no cyclisation occurred and the reduced nitrostyrene **250** was observed by ^{1}H NMR (Scheme 80). A likely explanation for this is that the strongly electron withdrawing nitro group makes the imine lone pair unavailable for protonation. It is known that for a nitro-Mannich reaction to occur the imine must be protonated prior to the nitronate attacking.[4] Also β-nitroamines are known to undergo retro-addition so it is feasible that the tetrahydroquinoline could be formed but then rapidly undergoes fragmentation to the nitroalkane.

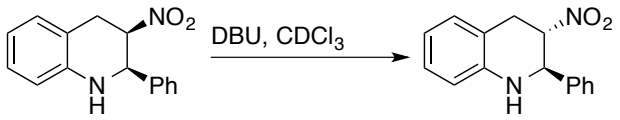


Scheme 80: Unsuccessful cyclisation of *p*-NO_2 substituted nitrostyrene **199m**.

3.12 Nitro Group Transformations

As the nitro group is a powerful synthetic handle, some functional group manipulations were investigated.

The *cis*-tetrahydroquinoline **175** could be converted to the *trans*-tetrahydroquinoline **160** by treatment with a base as per Zhou *et al*.[71] Indeed when tetrahydroquinoline **175a** was treated with DBU in $CHCl_3$ for 16 h the *trans*-tetrahydroquinoline **160a** was given in a 90% conversion by ^1H NMR (Scheme 81). After purification by column chromatography, the *trans*-tetrahydroquinoline **160a** was isolated in a yield of 72%, with no erosion of enantiopurity, as one diastereomer.

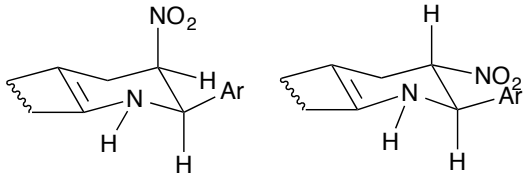


cis-**175a**
92% *ee*

trans-**160a**
72% yield
92% *ee*

Scheme 81: Conversion to the *trans*-diastereomer **160a**.

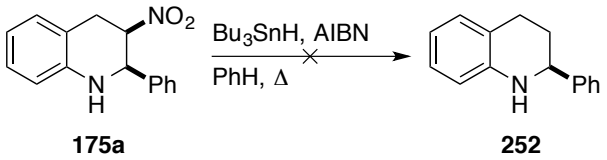
The epimerisation is probably driven by the removal of an axial substituent, giving the thermodynamically preferable *trans* stereochemistry with all equatorial substituents (Figure 13).



cis - **175** *trans* - **160**

Figure 13: Three dimensional structure of *cis*-**175a** and *trans*-**160a**.

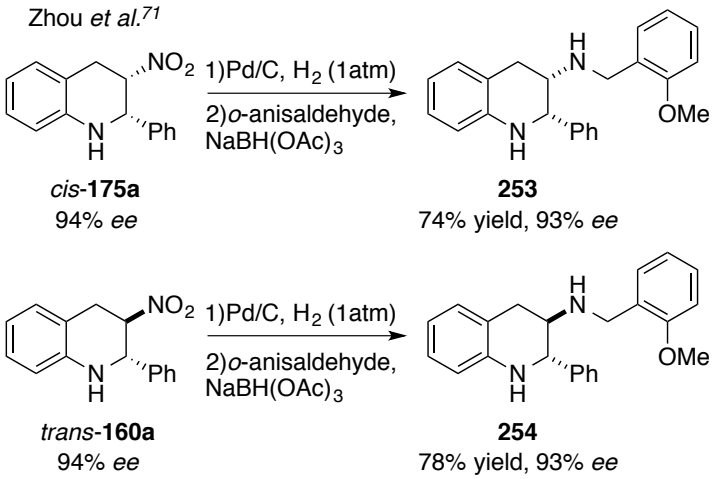
Radical denitration was studied; using the conditions described by Dixon *et al*. unfortunately only decomposition of the starting material occurred (Scheme 82).[60]



175a **252**

Scheme 82: Attempted radical denitration of tetrahydroquinoline **175a**.

The nitro group can also be reduced to the amine using Fe/HCl or Pd/C and H_2 as described by Zhou *et al*.[71] with only a small erosion in enantiopurity. The corresponding amines **253** and **254** can then used to make substance P agonists that have been reported by Pfizer.[111] Our method of making enantioenriched tetrahydroquinolines **175** and **160** therefore constitutes a formal synthesis of these substance P agonists too, but as the opposite enantiomer (Scheme 83).

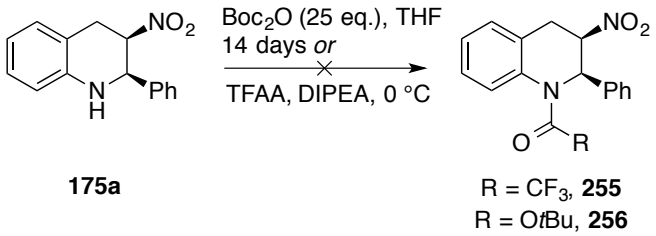


Scheme 83: Reduction of tetrahydroquinolines **175a** and **160a** to amine **253** and **254** in the formal synthesis of substance P agonists.

3.13 Determination of Absolute Stereochemistry

Protection of the tetrahydroquinoline **175a** as a *N*-Boc or *N*-trifluoroacetamide was investigated; these products might be crystalline and give suitable crystals for X-ray structures.[73] If an X-ray crystal is obtained then the absolute stereochemistry could be assigned by anomalous dispersion techniques. Unfortunately both protection procedures did not give the desired protected tetrahydroquinolines **255** or

256, only recovered starting material, with some epimerisation of the nitro stereocentre (Scheme 84).



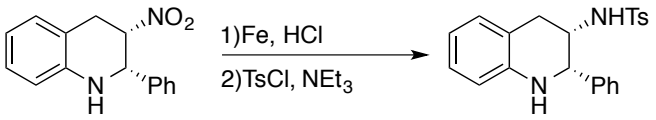
175a

R = CF_3, **255**
R = O*t*Bu, **256**

Scheme 84: Attempted protection of tetrahydroquinoline **175a**.

During this work Zhou *et al*.[71] had obtained X-ray crystals from the tosyl protected *cis*-3-aminotetrahydroquinoline **176**, made from *cis*-3-nitrotetrahydroquinoline **175a** (Scheme 85) and anomalous dispersion techniques determined the (*S*,*S*) stereochemistry. The tetrahydroquinolines made by our method were then assigned by comparison of the optical rotations and found to be (*R*,*R*) stereochemistry.

Zhou *et al*.[71]



175a **176**

>99% *ee* after crystallisation
Assigned as *cis*-(*S*,*S*)

Lit. **175a** 94% *ee*
$[\alpha]^{25}_D$= -84.3 (c = 0.17, $CHCl_3$)

This Work: **175a** 97% *ee*
$[\alpha]^{25}_D$= +85.9 (c = 0.15, $CHCl_3$)

Scheme 85: Reported synthesis of amine **176** and comparison of optical rotations of parent tetrahydroquinoline **175**.

Alternatively Maity *et al*. had reported the assignment of the absolute and relative stereochemistry of *trans*-tetrahydroquinoline **160** by X-ray diffraction and further confirmed by comparison of optical rotation with

Zhou *et al*.[71] Hence the optical rotation of the *trans*-tetrahydroquinoline **160a** made by epimerisation of the *cis*-tetrahydroquinoline could be used as further confirmation of the absolute and relative stereochemistry (Figure 14).[67]

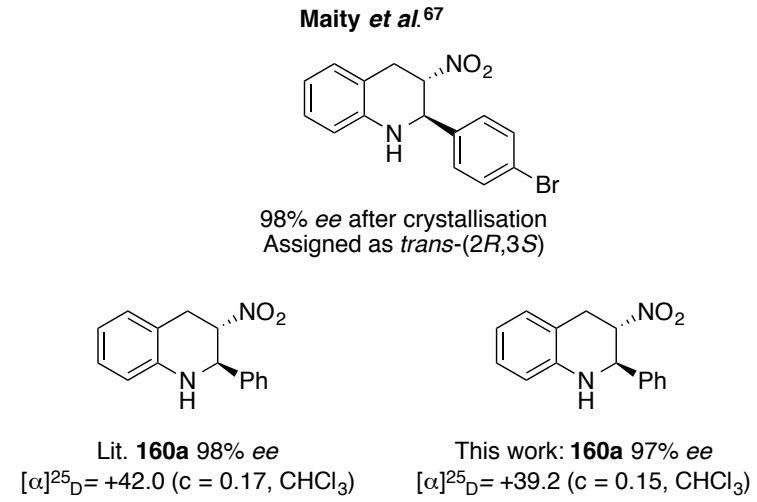
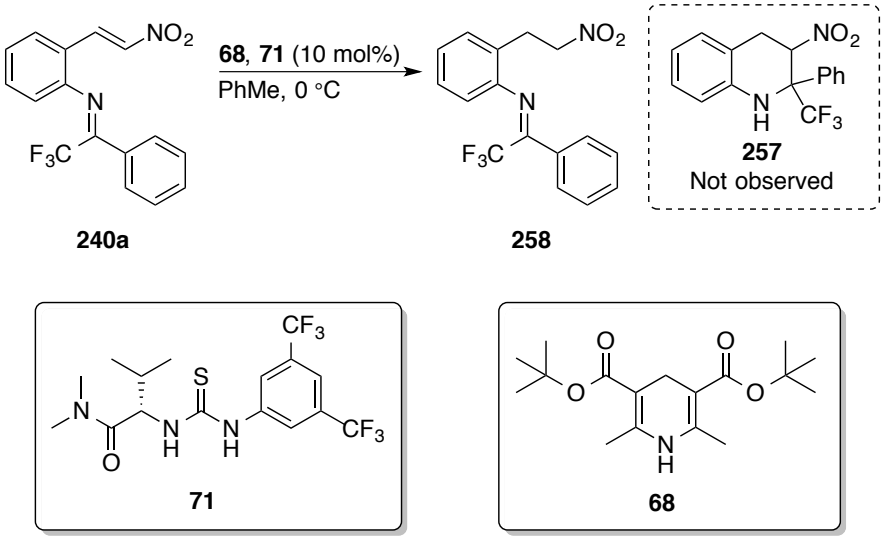


Figure 14: Comparison of optical rotations for *trans*-tetrahydroquinoline **160a**.

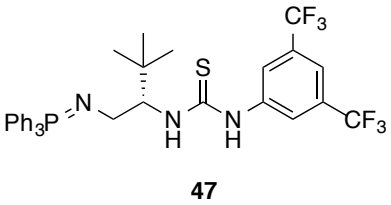
3.14 Ketimine Electrophile

Cyclisation of ketimine **240a** was attempted using the same catalyst and hydride source as previously described. None of the desired tetrahydroquinoline **257** was observed by ^{1}H NMR, only reduction of the nitrostyrene to the nitroalkane **258** (Scheme 86). A potential explanation for this is once again the strongly electron withdrawing groups on the imine prevent effective lone pair protonation to an iminium intermediate or that a retro reaction occurs and then subsequent protonation of the nitronate to the nitroalkane. Another potential explanation is simply that the ketimine is unreactive.



Scheme 86: Organocatalytic reduction of tethered ketimine **240a**.

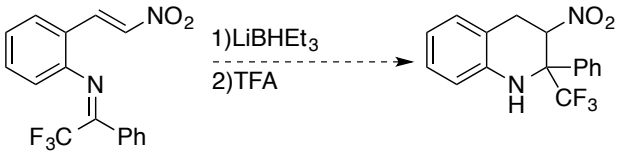
Ketimines are known to be difficult substrates in both standard nitro-Mannich chemistry and the organocatalytic variants. If the issue is simply that ketimine **240a** is not a suitable substrate for this catalyst, Dixon *et al*. have described the use of phosphazenes bound to a thiourea (Figure 15) as an effective catalyst for ketimines in the nitro-Mannich reaction, and this could be investigated for our substrate. [26]



47

Figure 15: Phosphazene catalyst **47** used for ketimine nitro-Mannich reaction.

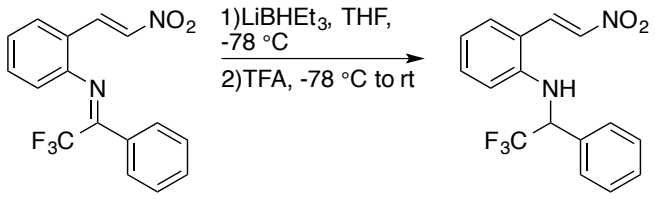
As the cascade was not triggered using the Hantzsch ester **68** and thiourea **71** combination, addition of superhydride as the hydride source was investigated, which would give the racemic tetrahydroquinoline **257** (Scheme 87).



240a **257**

Scheme 87: Proposed nitro-Mannich reaction using ketimine **240a** and $LiBHEt_3$.

This would also give some insight into whether it was an ineffective catalyst or the substrate that was the issue. Surprisingly, when Superhydride/TFA was used, little of the desired tetrahydroquinoline (<5%) was observed by ^1H NMR, but amine **259** was isolated in a yield of 89% (Scheme 88).



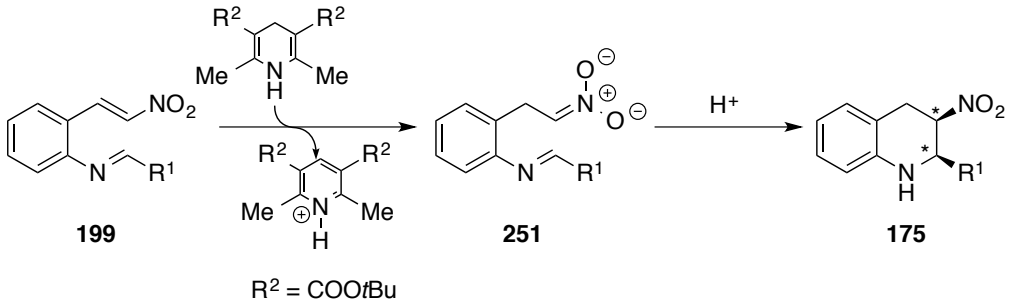
240a **259**
89% yield

Scheme 88: Addition of $LiBHEt_3$ to ketimine **240a**.

It is difficult to rationalize why the replacement of the hydride source has such a pronounced effect on the site of nucleophilic attack, especially as both were previously shown to preferentially add in a 1,4 fashion using nitrostyrene **199a** as a substrate.

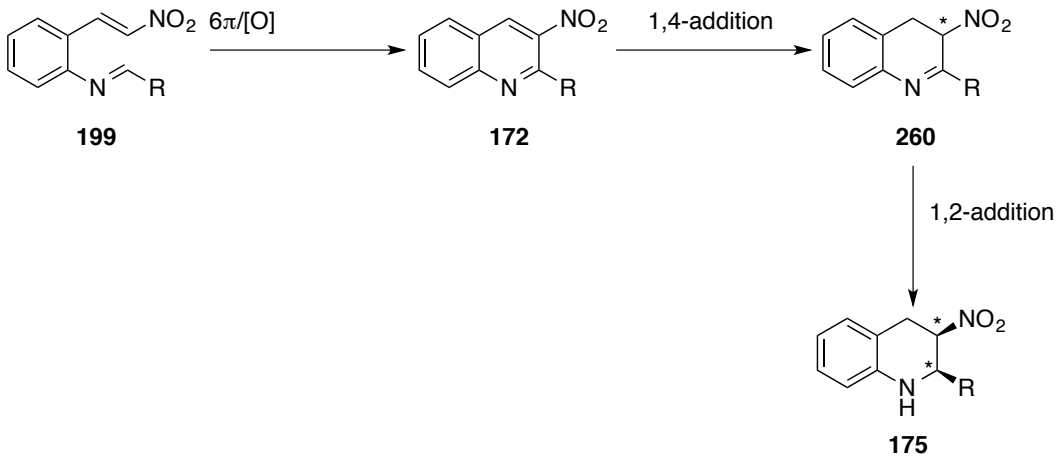
3.15 Mechanism of Tandem Cyclisation

The mechanism is thought to be similar to an organocatalytic reductive nitro-Mannich reaction; 1) 1,4 addition of a hydride to the nitrostyrene **199** 2) protonation of the imine **251** to give the activated iminium and 3) attack by the nitronate onto the iminium, guided by the thiourea catalyst to give tetrahydroquinoline **175** (Scheme 89).



Scheme 89: Proposed mechanism of reductive tandem cyclisation.

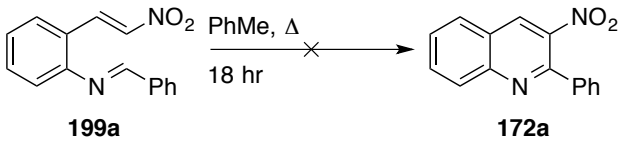
An alternative mechanism could be proposed, as previously 3-nitroquinolines **172** have been organocatalytically hydrogenated to give the desired *cis*-tetrahydroquinolines **175**. The mechanism would be as follows: 1) 6π electrocyclisation and oxidation to the quinoline **172**, 2) 1,4-addition of a hydride to give the dihydroquinoline **260** and 3) 1,2-addition of another hydride to give tetrahydroquinoline **175** (Scheme 90).



Scheme 90: Alternative mechanism to give tetrahydroquinoline **175**.

This mechanism is less plausible as only one equivalent of a hydride and proton source is used in the reaction; a dearomatisation of quinoline **172** would need two. Also the reaction is not affected if performed under an inert atmosphere, so doesn't require an external oxidant such as air. The 6π cyclisation/oxidation of α,β-unsaturated esters requires elevated temperatures, and so nitrostyrene **199** was heated to 120 °C in PhMe to see if electrocyclisation occurs (Scheme 91).[112] No reaction was

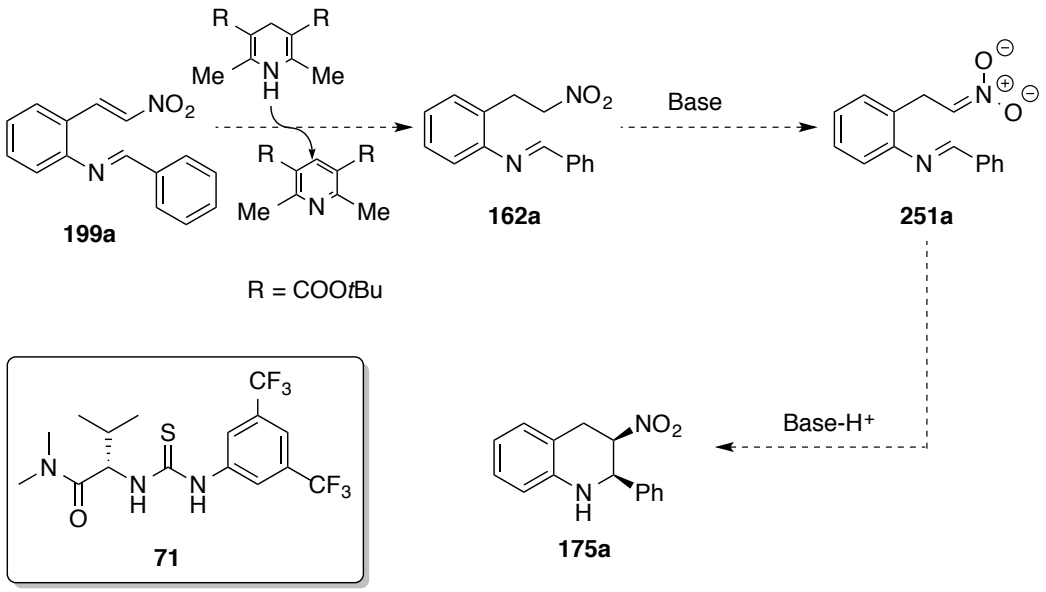
observed when monitoring the reaction by ^{1}H NMR and TLC, providing evidence that a quinoline intermediate is unlikely.



199a **172a**

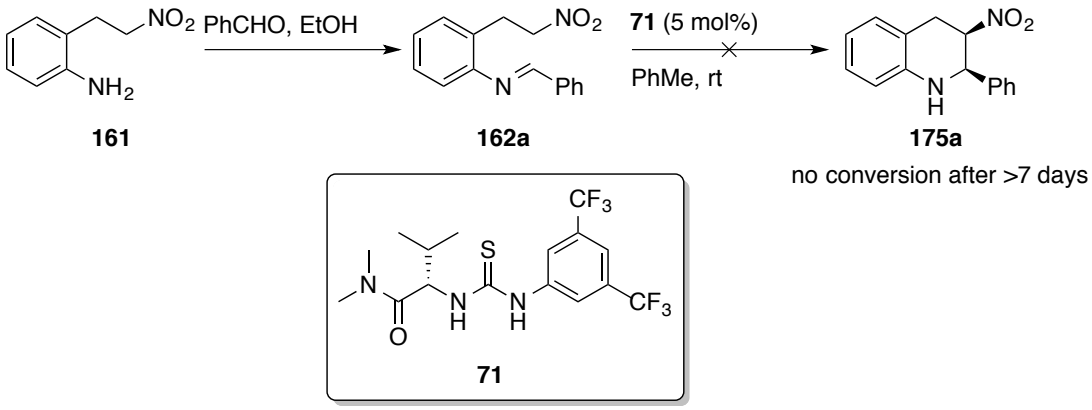
Scheme 91: Attempted thermal cyclisation of nitrostyrene **199a**.

Another potential pathway is reduction of the nitrostyrene **199a** to nitroalkane **166a**. The nitroalkane **162a** can then form the nitronate and react to give tetrahydroquinoline **175a** as described by Maity *et al.* (Scheme 92).[67]



Scheme 92: Alternative mechanism with nitroalkane **162a** as an intermediate.

When nitroalkane **162a** was stirred with 5 mol% thiourea **71** no conversion was observed by ^{1}H NMR or TLC over >7 days (Scheme 93). It is feasible to infer from this observation that the cascade cyclisation occurs with a rapid nitro-Mannich reaction after generation of the nitronate, not a cyclisation after nitroalkane **162a** is generated.



Scheme 93: Attempted cyclisation with nitroalkane **162a**.

3.16 Origin of Stereoselectivity

The reaction is thought to proceed *via* an intramolecular tethered Zimmerman-Traxler transition state when either Superhydride/TFA or **68** and **71** are used. This transition state is similar to what was proposed by Xu *et al*. in their synthesis of tetrahydroquinolines (Figure 16).[65]

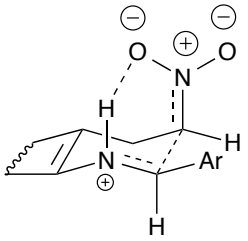
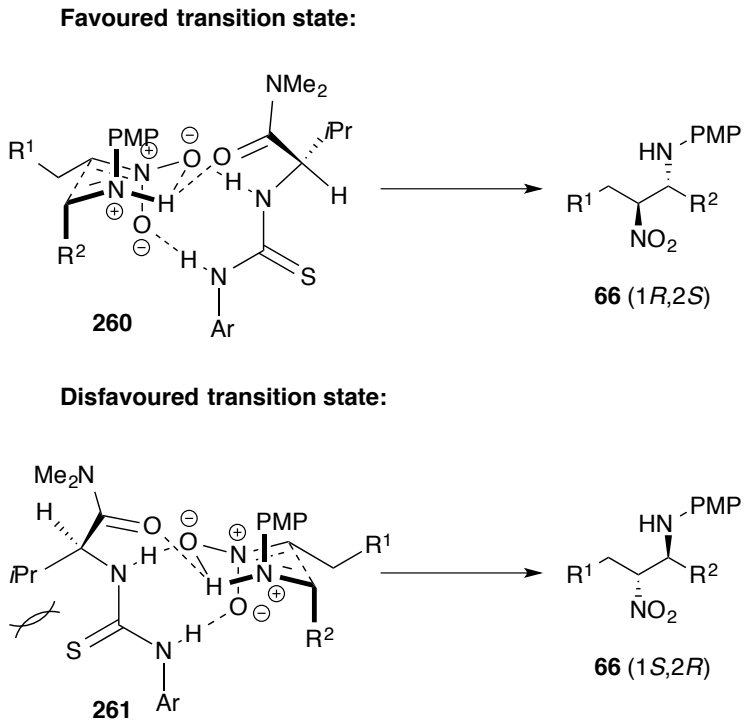


Figure 16: Proposed transition state account for sense of diastereoselection.

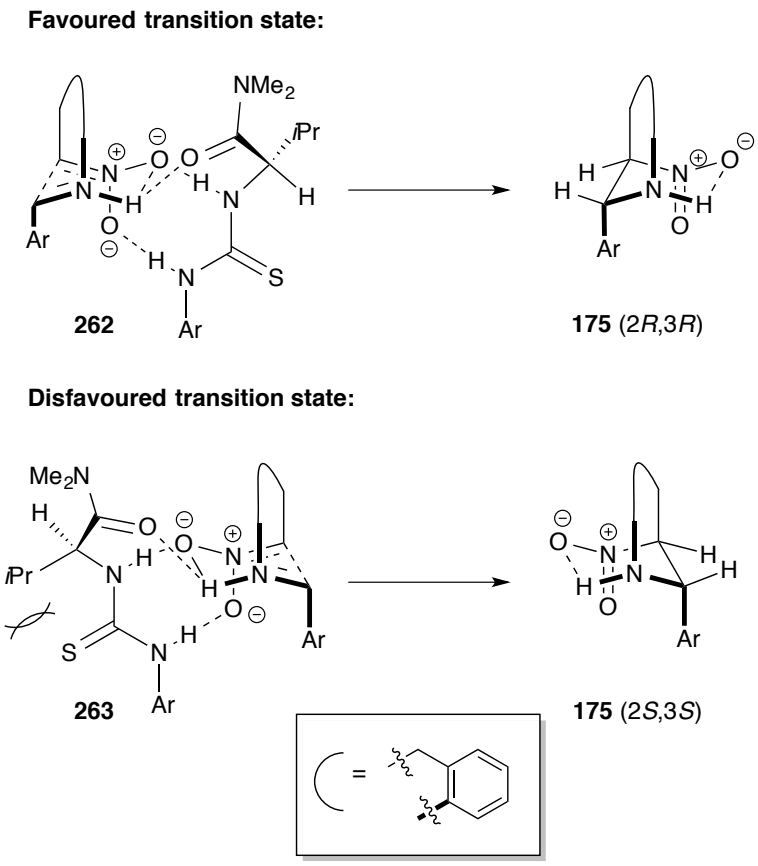
To account for the enantioselecitivity when thiourea **71** is used as a catalyst we can draw a comparison with the work previously described by Anderson *et al*. and Jacobsen *et al*. The proposed transition state for an untethered nitro-Mannich reaction is thought to have two hydrogen bonds between the nitronate and the thiourea and another hydrogen bond between the amide and iminium species (Scheme 94). Jacobsen *et al*. had proposed that the most stable transition state for thiourea **71** is when the C-H bond is in the same plane to the C=S bond as shown in transition state **260** giving the (1*R*,2*S*) enantiomer. In order to get the opposite enantiomer the *iso*-propyl group is in the same plane as the C=S bond as

shown in transition state **261**, as there are unfavorable steric interactions between the two groups it is thought to be the least stable transition state.[113]



Scheme 94: Proposed origin of enantioselectivity for untethered examples.

We can then apply this model to our system, but where the imine is tethered to the nitronate. In the same manner as above we have the same hydrogen bonds between the thiourea catalyst and the closed hydrogen bonded transition state, but the group adjacent to the nitronate occupies a *pseudo* axial position instead of the *pseudo* equatorial as it is linked to the imine. The favoured transition state **262** gives rise to the observed (2*R*,3*R*) enantiomer, while the disfavored transition **263** state gives rise to the opposite (2*S*,3*S*) enantiomer (Scheme 95).

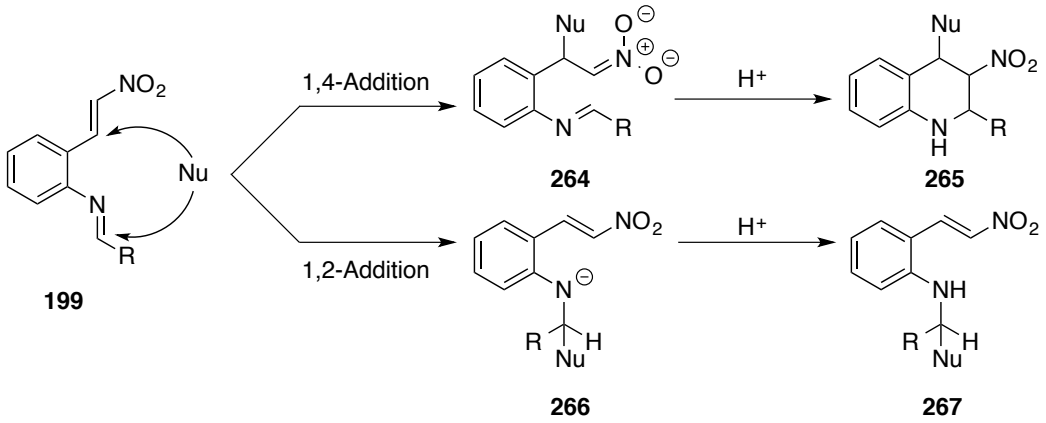


Scheme 95: Modified transition state for tethered examples.

Following the work by List *et al*. and Anderson *et al*. it is assumed that the thiourea catalyst also controls the enantioselective addition of the hydride to the nitrostyrene.[32, 33] In our case this is unimportant, as a new stereocenter is not produced in the conjugate addition step.

3.17 Synthesis of Densely Functionalised Tetrahydroquinolines

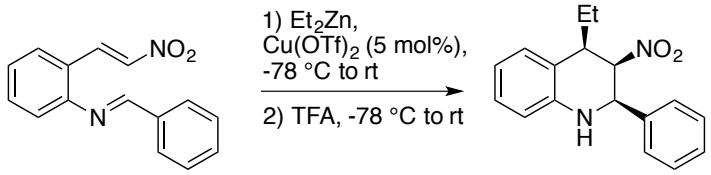
An extension to the intramolecular nitro-Mannich reaction was investigated, whereby the trigger to the cascade reaction was a carbon based nucleophile. The use of dialkylzincs in the presence of a Cu(I) catalyst has been shown to form the nitronate *in situ*, which can then be used in the nitro-Mannich reaction (see Scheme 22).[44] It was thought that dialkylzincs may selectively add to the nitrostyrene, not the imine (Scheme 96).[114] Potentially solvent effects may lead to different products.



Scheme 96: Potential reaction pathways between nitrostyrene **199** and organozinc reagents.

This reaction was investigated using **199a** as the model system. Addition of diethylzinc in a selection of solvents provided the desired tetrahydroquinoline in good yields and high diastereoselectivity. Use of Et_2O as the reaction solvent provided a modest increase in the *dr*, providing the tetrahydroquinoline **268a** as a single diastereomer after column chromatography (Table 11).

Table 11: Intramolecular nitro-Mannich reaction with dialkylzincs.



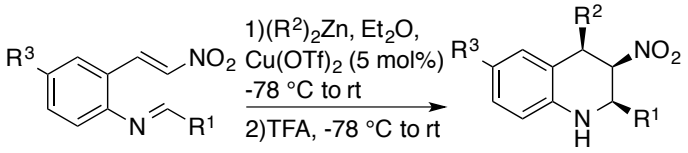
199a **268a**

Solvent	Yield	*dr*[a,b]
THF	62	7:3 (9:1)
PhMe	64	7:3 (9:1)
Et_2O	62	>95:5 (>95:5)

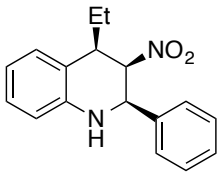
[a]Calculated by ^{1}H NMR of the material after column chromatography. [b]Numbers in parentheses correspond to the *dr* calculated by ^{1}H NMR of the crude material.

A selection of tethered nitrostyrenes were used in the conditions previously described, giving the desired tetrahydroquinolines **268** in good yields and very good diastereoselectivity (Table 12). A noted exception was when *p*-NO_2 nitrostyrene **199m** was used as a substrate.

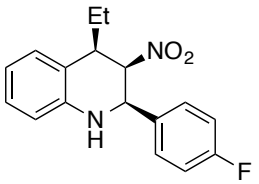
Table 12: Substrate scope of dialkylzinc triggered cascade cyclisation.



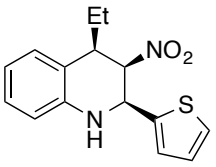
199 **268**



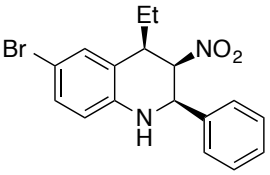
268a, 62% yield, >95:5 *dr*



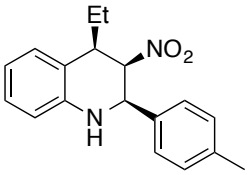
268b, 80% yield, 90:10 *dr*



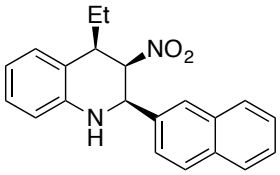
268c, 53% yield, >95:5 *dr*



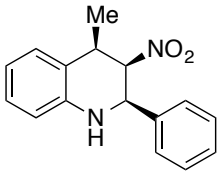
268d, 80% yield, 90:10 *dr*



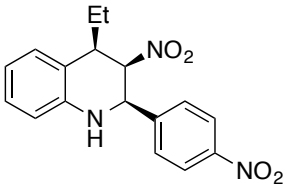
268e, 73% yield, >95:5 *dr*



268f, 86% yield, >95:5 *dr*



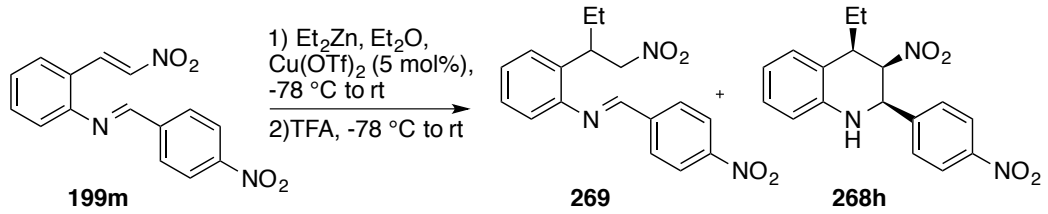
268g, 52(0)[b]% yield, >95:5 *dr*



268h, 0(40)[c]% yield

[a]Calculated by ^{1}H NMR, [b]$AlMe_3$ used instead of Me_2Zn, [C]conversion by ^{1}H NMR.

Like with the organocatalytic nitro-Mannich cyclisation, when the *para*-nitro substituted aryl **199m** was used, the desired tetrahydroquinoline was not isolated. When the crude reaction mixture was analysed by ^{1}H NMR it showed complete conversion to the conjugate addition product **269h** and 40% conversion to the cyclised product **268h**, but neither **269h** nor **268h** could be isolated by column chromatography on silica gel (Scheme 97). It is thought that incomplete cyclisation may have occurred due to the imine lone pair being deactivated by the *p*-NO_2 group, but also the product may be prone to a retro nitro-Mannich reaction.



Complete consumption of **199m**
60:40 ratio of products by ^{1}H NMR of the crude material

Scheme 97: Incomplete cyclisation when R^1 = *p*-NO_2Ar.

3.18 Assignment of Relative Stereochemistry

The relative stereochemistry was assigned by ^{1}H NMR based on the coupling constants between H_a and H_b, and between H_b and H_c. The major diastereomer for **268d** had a J_{ab} = 2.6 Hz and a J_{bc} = 3.3 Hz while the minor diastereomer had a J_{ab} = 2.9 Hz and a J_{bc} = 4.7 Hz.

If we assume a chair-like confirmation for tetrahydroquinoline **268d**, then using the Karplus equation we would get a predicted ^3J value of ~4 Hz when the dihedral angle between H_aH_b or H_bH_c = ~60°.[115] Similarly when the dihedral angle between H_aH_b or H_bH_c = ~180° we can expect the ^3J value to be ~8 Hz. The tetrahydroquinolines **270**, **271**, **273** and **274** have dihedral angles between H_aH_b and H_bH_c that are ~60° and so have predicted coupling constants in agreement with the experimental values (Figure 17). The tetrahydroquinolines **272a** and **272b** have dihedral angles between H_aH_b that are ~180° and so have predicted coupling constants that are not in agreement with the experimental values.

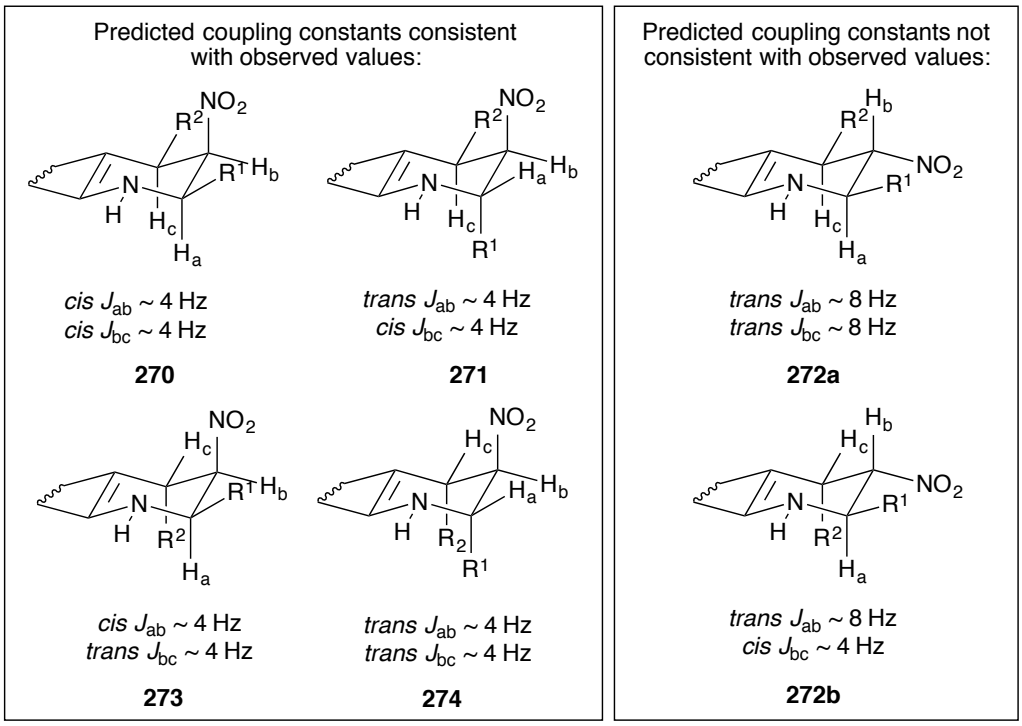


Figure 17: Possible diastereomers and their coupling constants.

Energetically the *trans*,*trans* diastereomer **274$_{ax,ax}$** appears to be unlikely as it suffers from unfavorable 1,3-diaxial interactions between R^1 and R^2. A more stable conformation would be **274$_{eq,eq}$** as this removes all the axial substituents (Figure 18). Conformation **274$_{eq,eq}$** has H_a antiperiplanar to H_b so we expect a J_{ab} = ~ 8 Hz, and H_b antiperiplanar to H_c so we expect a J_{bc} ~ 8 Hz. Due to this the *trans*,*trans* diastereomer **274** is removed as a possibility.

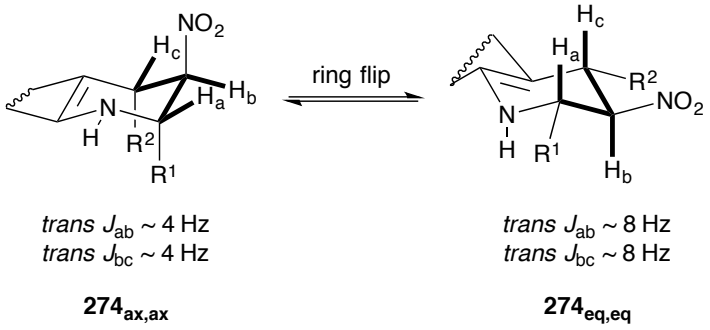
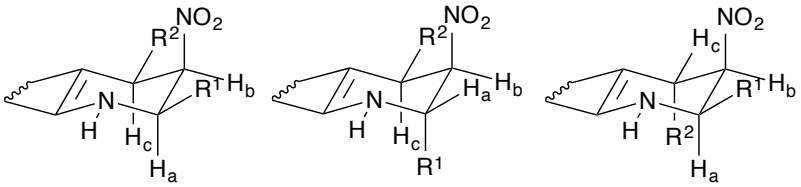


Figure 18: Possible conformations of *trans*,*trans* tetrahydroquinoline **274**.

There are therefore three possible diastereomers that could be either the major or minor diastereomer **268**. These could be *cis*,*cis* **270**, *trans*,*cis*

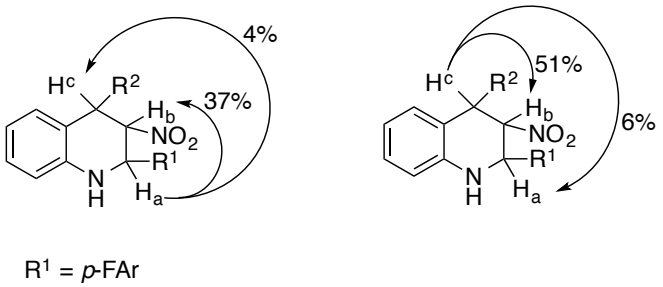
271 or *cis*,*trans* **273** as each of these have J_{ab} = ~4 Hz and J_{bc} = ~ 4 Hz (Figure 19).



cis,*cis* **270** *trans*,*cis* **271** *cis*,*trans* **273**

Figure 19: Three most likely stereoisomers for **268d$_{major}$** or **268d$_{minor}$**.

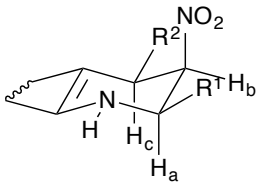
An nOe experiment was performed on the major diastereomer, as if the major diastereomer is either *cis*,*trans* **273** or *trans*,*cis* **271** then no enhancement should be observed between H_a and H_c. When H_a was irradiated (4.75 ppm) there was an enhancement of H_b = 37% and H_c = 4% (Figure 20). When H_c was irradiated (3.20 ppm) there was an enhancement of H_b = 51% and H_a = 6%. The observed enhancements are consistent with similar 2,3,4-trisubstituted tetrahydroquinolines in the literature, particularly *cis*,*cis* diastereomers.[74]



R^1 = *p*-FAr

Figure 20: nOe enhancements of H_a and H_c.

As there are through-space interactions between H_a and H_c the major diastereomer was assigned as the *cis*,*cis* relative stereochemistry **270** (Figure 21).

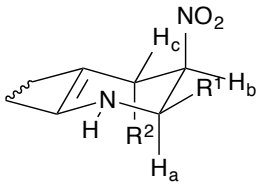


cis,*cis*

268d$_{major}$ = configuration **270**

Figure 21: Proposed structure of the major diastereomer.

On the basis that there are no reports of *trans*,*cis* tetrahydroquinolines in the literature and there are previous reports of similar reactions giving *cis*,*trans* tetrahydroquinolines[65, 73] the minor diastereomer **268d$_{minor}$** is tentatively assigned as *cis*,*trans* **273** (Figure 22).



cis,*trans*

268d$_{minor}$ = configuration **273**

Figure 22: Proposed stereochemistry of the minor diastereomer.

3.19 Origin of Diastereoselectivity

The origin of the *cis*,*cis*-diastereoselectivity is thought to occur by a Zimmerman-Traxler type transition state **275** (Figure 23). The alkyl and aryl groups are thought to be on the thermodynamically preferable equatorial position, whilst the nitro group is axial and internally hydrogen-bonded to the iminium ion in a manner similar to previous nitro-Mannich reactions.[4] The observed *cis*,*cis*-stereochemistry is in contrast to Xu *et al*. in their organocatalytic synthesis of *cis,trans*-tetrahydroquinolines **158.** The relative stereochemistry of these *cis,trans*-tetrahydroquinolines **158** were assigned by single crystal X-ray analysis. They suggested a transition state that placed the –CH_2COPh substituent on the pseudo-axial position to account for their *cis,trans*-stereochemistry.[65] This is

energetically less favorable than our proposed transition state as theirs suffers from 1,3-diaxial interactions between H_a and the CH_2COAr group.

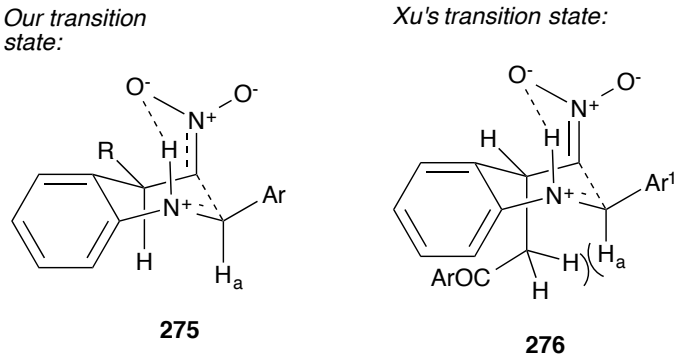
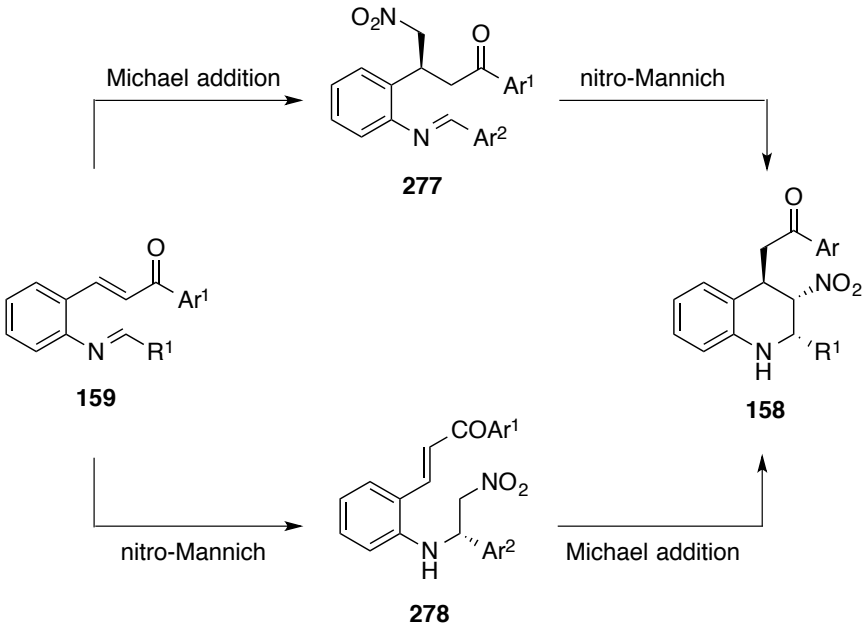


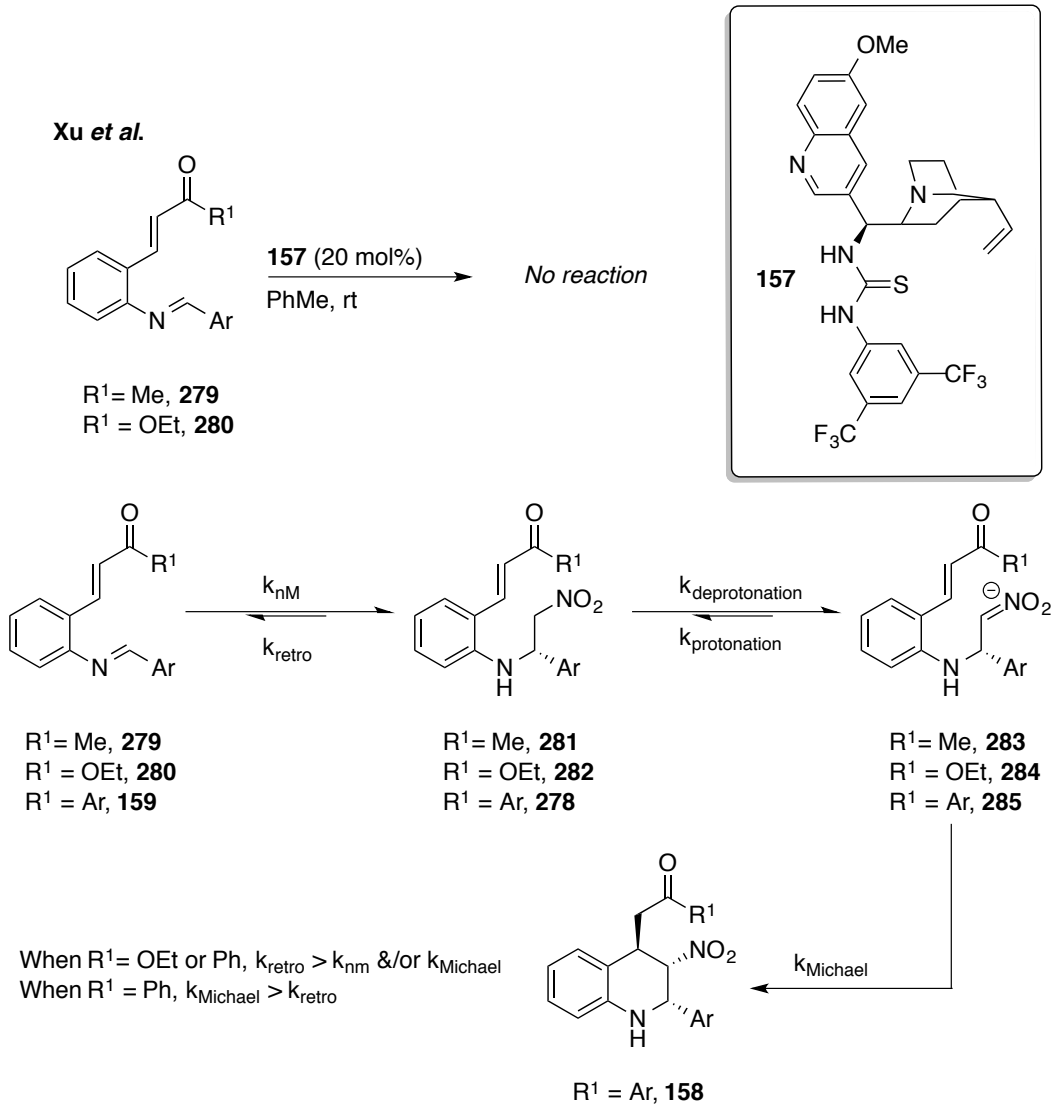
Figure 23: Proposed transition state to account for the sense of diastereoselection and Xu's.

Additionally the anomalous report by Maity *et al*. (Scheme 41) that using the same catalyst as Xu *et al*. they obtained the *trans*-tetrahydroquinoline not the *cis* in a similar transformation implies that their mechanism of cyclisation may be a nitro-Mannich/Michael sequence, not a Michael/nitro-Mannich reaction (Scheme 98).[67]



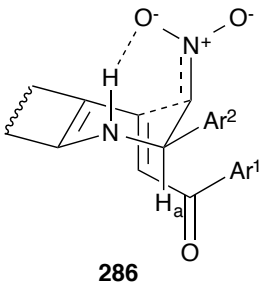
Scheme 98: Two possible pathways for Xu's synthesis of tetrahydroquinoline **158**.

A series of control experiments were performed by Xu *et al*. (Scheme 99), they used these as part of their mechanistic reasoning for a Michael/nitro-Mannich mechanism. As no reaction occurred when R^1 = Me **279** or OEt **280**, they said the phenyl group was essential. They claimed the Michael addition is the rate-determining step and so it is a Michael/nitro-Mannich sequence. However they do not account for or discuss the possibility that the nitro-Mannich reaction is reversible and so if **279** or **280** are inactive, it might be that the 2nd step or 3rd step ($k_{deprotonation}$ and $k_{michael}$) never occur or are much slower than retro-addition (k_{retro}), hence no reaction is observed. Therefore their control experiments do not support either mechanism.



Scheme 99: Observed inactivity of **279** and **280**.

We can therefore imply that their mechanism might be a nitro-Mannich/Michael sequence with the proposed transition state **286** (Figure 24). This transition state also suffers from 1,3-diaxial interactions between H_a and =CHCOPh but the revised transition state **286** is thought to be energetically lower,[116] while retaining the intramolecular hydrogen bonding between the nitronate and amine.



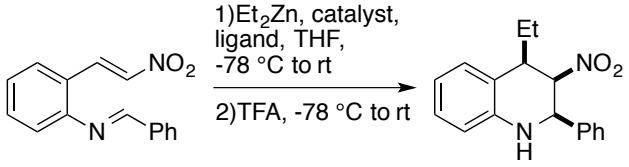
286

Figure 24: Proposed revised transition state **286**.

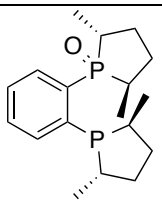
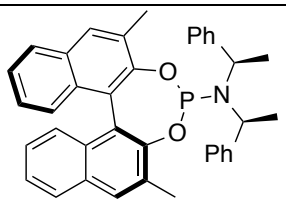
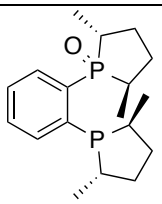
3.20 Asymmetric Synthesis

The asymmetric cyclisation was then investigated with chiral ligands BOZPhos **86** and phosphoramidite **131** (in collaboration with visiting student Matus Diveky), as these ligands have previously shown excellent activities in asymmetric nitro-Mannich reactions, when dialkylzincs are used.[44, 117] In all cases the product was isolated as the racemate (Table 13).

Table 13: Enantioselective addition of diethylzinc to nitrostyrene **199a**.

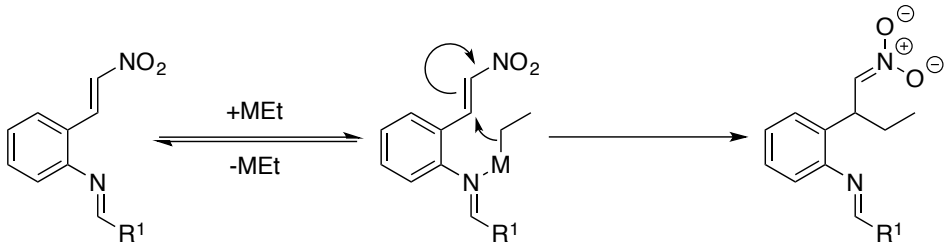


199a **268a**

Ligand	Catalyst	Yield	*ee*[a]
	$(CuOTf)_2$.PhMe (5 mol%)	21	0
	$Cu(OTf)_2$ (5 mol%)	62	0
	$Cu(OTf)_2$ (5 mol%)	21	0

[a]Enantiomeric excess determined by chiral HPLC.

The absence of enantioselectivity is thought to be due to the imine substituent *ortho* to the nitrostyrene. One explanation is that the imine lone pair may be coordinating with the Cu catalyst, preventing effective binding of phosphine **86** or **131** to the reaction center (Scheme 100). Previous nitro-Mannich chemistry has indicated that *ortho* substituents on the nitrostyrene are not tolerated when dialkylzincs are used as the nucleophile; this reaction runs contrary to that observation and so this reaction may have a different pathway.[52]



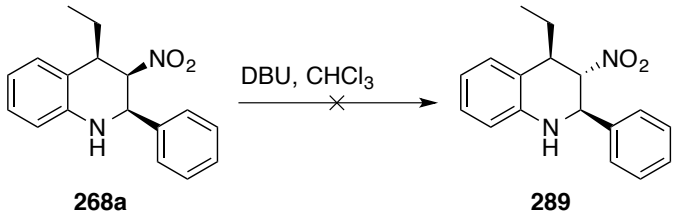
Scheme 100: Proposed Intramolecular conjugate addition of alkyl group *via* imine-metal complex **287**.

Also, Ojima *et al*. noted that an *ortho* substituent adjacent to a nitrostyrene decreased the enantioselecitivty of copper catalyzed asymmetric conjugate additions of dialkylzincs to nitrostyrenes; in most cases this was attributed to steric interactions.[118] The steric bulk of the imine group is not sufficiently large to fully explain the reaction occurring racemically, but may contribute to the lack of asymmetric induction.

As there was no asymmetric induction and limited time, this work was halted. It might be possible with extensive screening of ligands that an asymmetric variant is possible.

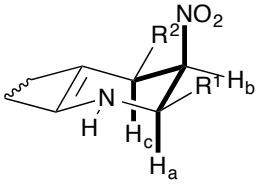
3.21 Transformations of Densely Functionalised Tetrahydroquinolines

An attempt to convert tetrahydroquinoline **268a** to the *trans,trans* diastereomer **289** by epimerisation at the nitro center was not successful (Scheme 101). All that was observed was degradation of the starting material and a visible colour change to red, indicating the elimination of HNO_2.



Scheme 101: Attempted formation of *trans,trans*-tetrahydroquinoline **289**.

Base mediated denitration is rare when it is not adjacent to an electron-withdrawing group.[96] These systems may decompose so readily because of the dense substitution pattern; there is a large amount of steric compression and elimination to a planar product relieves this strain. The *cis*,*cis* relationship also means that both protons are antiperiplanar to the nitro group and therefore perfectly placed for an E_2 type elimination pathway (Figure 25).

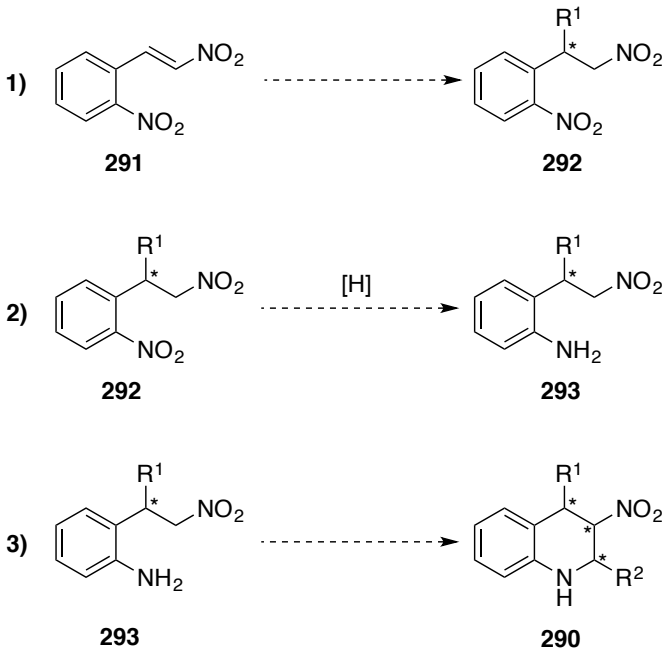


268

Figure 25: Antiperiplanar relationship between NO_2 and H_a or H_b as potential elimination pathways.

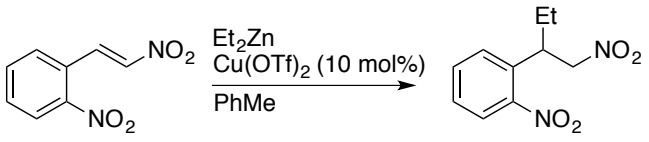
3.22 Alternative Intramolecular Nitro-Mannich Reactions

An alternative route to enantioenriched densely functionalised tetrahydroquinolines **290** was hypothesised, whereby 1) nitrostyrene **291** is converted to nitroalkane **292** by an asymmetric conjugate addition reaction, 2) the aryl nitro is then reduced to give aniline **293**,[66] 3) an imine formation/intramolecular nitro-Mannich reaction would provide a facile route tetrahydroquinoline **290** (Scheme 102). Not only would this route provide an opportunity for enantioenriched tetrahydroquinolines, but may give different diastereomers to the tandem cyclisation although having the same sequence of steps.



Scheme 102: Proposed synthesis of densely functionalised tetrahydroquinoline **290**.

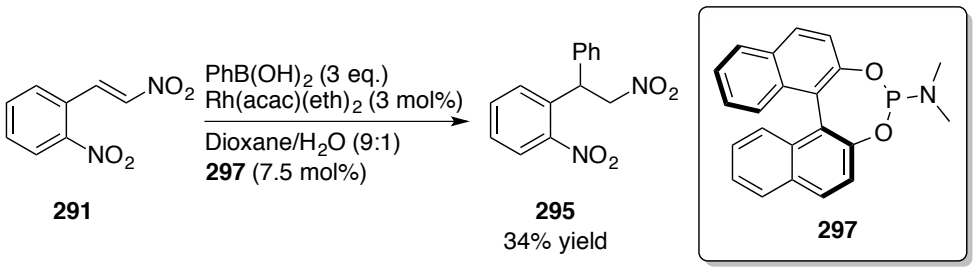
Addition of diethylzinc to nitrostyrene **291** in the presence of $Cu(OTf)_2$ gave nitroalkane **294** in a low yield of 17% (Scheme 103). This is not surprising considering nitrostyrene **291** bears an *ortho*-substituent. While this yield is un-optimized, its low yield highlights the deficiencies of a sequential strategy to the construction of densely functionalised tetrahydroquinolines using dialkylzinc as the nucleophile, and so a cascade reaction can be considered superior.



291 **294**
17% yield

Scheme 103: Preparation of nitroalkane **294**.

Use of an arylboronic acid in conjunction with a rhodium (I) catalyst would give an enantioenriched nitroalkane **295**. Reduction and then imine formation/cyclisation would give the desired tetrahydroquinoline **296** in a similar manner as above. Addition of phenylboronic acid to nitroalkene **291** using the procedure described by Feringa *et al.* gave the desired nitroalkane **295** in a poor yield of 34% (Scheme 104), unfortunately this reaction was extremely slow (up to 5 days for completion).[119]

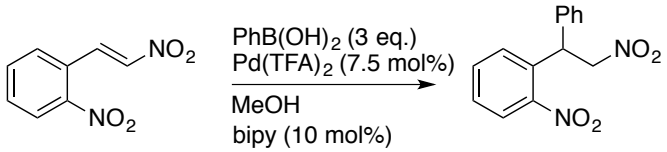


291 **295**
34% yield

297

Scheme 104: Synthesis of nitroalkane **295**.

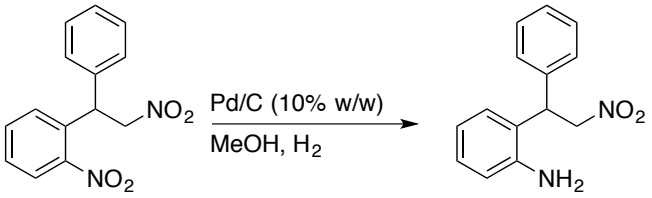
As this yield was low, an operationally simpler methodology described by Zhang *et al*. was tested that gave the desired nitroalkane **295** in a pleasing yield of 90%, in a more acceptable time of 2 days (Scheme 105).[120]



291 **295**
90% yield

Scheme 105: Palladium catalyzed carbopalladation of nitrostyrene **291**.

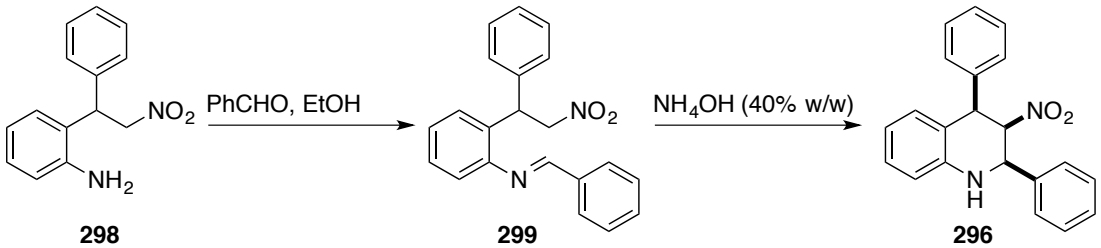
Reduction of the aryl nitro group using Pd/C and a H_2 balloon gave the desired aniline **298** in a quantitative yield (scheme 107).



295 **298**
100% yield

Scheme 107: Reduction of nitro **295** to aniline **298**.

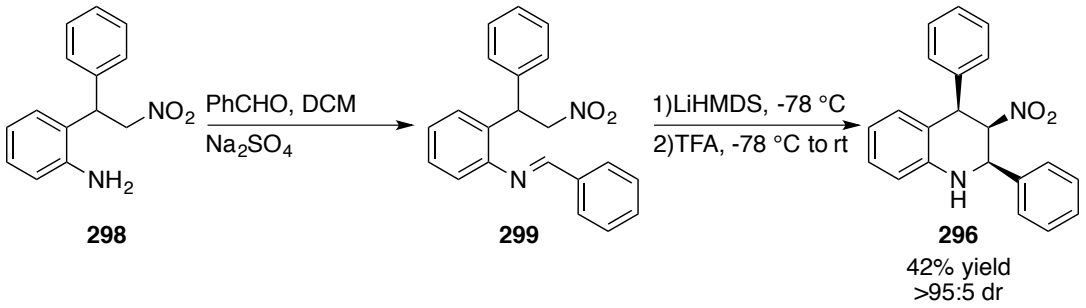
Nitroamine **298** was then condensed with benzaldehyde to give imine **299** after 48 hr. To the intermediate imine was added to aqueous NH_4OH as a base as described by Anderson *et al*.[66] The reaction mixture was stirred for 48 h to give the densely functionalised tetrahydroquinoline as a 1:1:1 mixture of diastereomers in the crude ^1H NMR (Scheme 108), but only the *cis*,*cis* (assigned as above) could be isolated pure in a yield of 24% (9:1 dr). The crude mixture was noted to be bright red, indicating that elimination of HNO_2 may have occurred.



298 **299** **296**
24% yield
9:1 dr

Scheme 108: Synthesis of tetrahydroquinoline **296** by an intramolecular nitro-Mannich reaction.

In an attempt to optimize this reaction, after imine formation the nitroalkane was deprotonated with LiHMDS at -78 °C and TFA added to promote the cyclisation, giving the *cis*,*cis*-tetrahydroquinoline **296** in a yield of 42% as one diastereomer (Scheme 109).

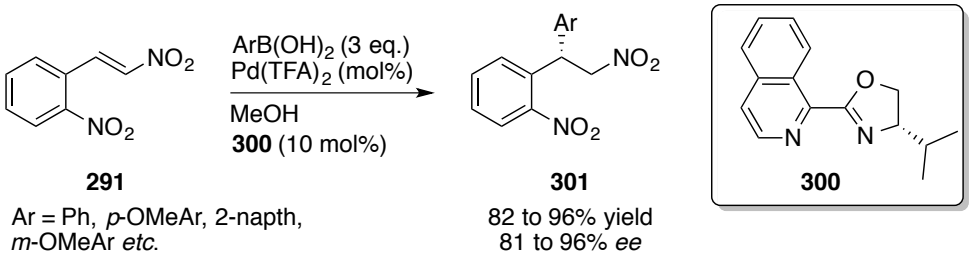


298 **299** **296**

42% yield
>95:5 dr

Scheme 109: Selective intramolecular nitro-Mannich reaction.

This result provides an expedient route to functionalised tetrahydroquinolines. Previous work by Zhang *et al*. shows that use of oxazoline ligand **300** would give the enantioenriched nitroalkane **301** and hence give the desired optically enriched tetrahydroquinoline **296** (Scheme 110).



291

Ar = Ph, *p*-OMeAr, 2-napth, *m*-OMeAr *etc*.

301

82 to 96% yield
81 to 96% *ee*

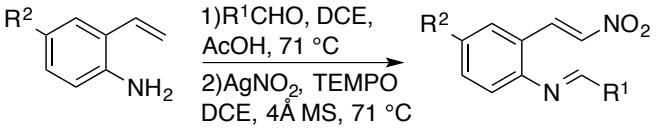
300

Scheme 110: Asymmetric variant of the carbometallation of nitrostyrenes.

4.0 Conclusion and Future Studies

4.1 Conclusion

It was found that nitrostyrene **199** could be made from 2-aminostyrenes **229** by condensation with an aldehyde and then radical nitration with $AgNO_2$/TEMPO. This procedure was usually high yielding, but it was limited to aryl and glyoxyl imines (Scheme 111).



229

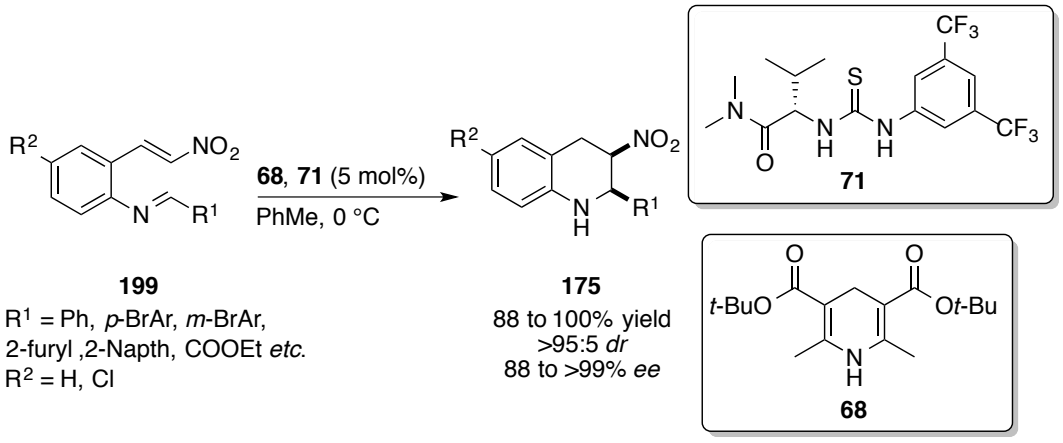
R^1 = Ph, *p*-BrAr, *m*-BrAr, 2-furyl, 2-Napth, COOEt *etc*.
R^2 = H, Cl, Br

199

15 to 97% yield

Scheme 111: Successful radical nitration route to nitrostyrene **199**.

These nitrostyrenes could then be used in a tandem organocatalytic conjugate addition nitro-Mannich reaction. Use of Hantzsch ester **68** with 5 mol% thiourea **71** gave the corresponding tetrahydroquinoline in high yields and excellent stereoselectivity (Scheme 112).



199

R^1 = Ph, *p*-BrAr, *m*-BrAr, 2-furyl ,2-Napth, COOEt *etc*.
R^2 = H, Cl

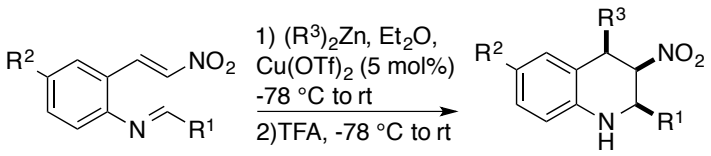
175

88 to 100% yield
>95:5 *dr*
88 to >99% *ee*

Scheme 112: Organocatalytic reductive cyclisation of nitrostyrene **199** to tetrahydroquinoline **175**.

Carbon based nucleophiles could also trigger a Michael/nitro-Mannich cascade cyclisation. Addition of diethylzinc gave the nitronate *in situ* and

then cyclisation occurred upon addition of TFA to give the densely functionalised tetrahydroquinoline **268** in high yields and diastereoselectivity (Scheme 113). A brief investigation to control the absolute stereochemistry was found to be unsuccessful.



199

R^1 = Ph, *p*-FAr, 2-Napth, 2-thiophen *etc.*
R^2 = H, Br
R^3 = Et, Me

268

52 to 86% yield
90:10 to >95:5 *dr*

Scheme 113: Michael/nitro-Mannich approach to densely functionalised tetrahydroquinolines **268**.

These new methodologies should provide a novel route to tetrahydroquinolines of biological interest and provide a starting point for investigating other nucleophiles to trigger this cascade reaction.

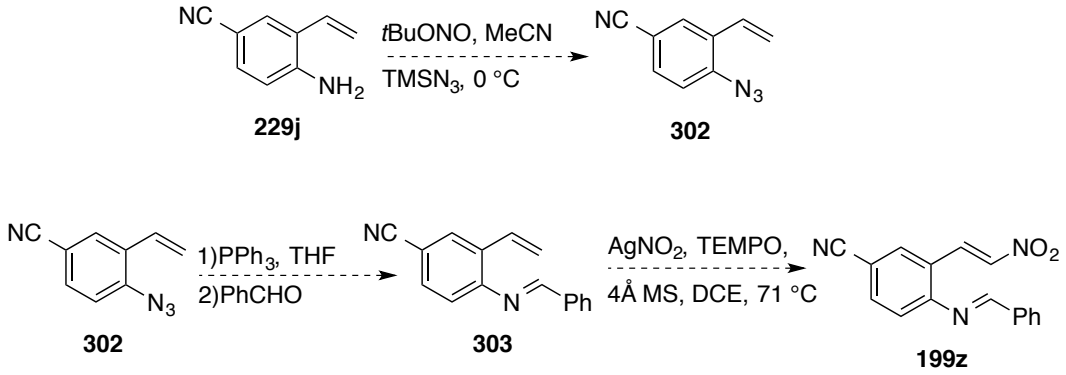
4.2 Future work

As the synthesis of the nitrostyrenes has been found to be high yielding, increasing the substrate scope could provide a more diverse array of tetrahydroquinolines, which could be useful for natural product synthesis. Other nucleophiles may provide new opportunities to investigate the intramolecular nitro-Mannich reaction. Two particularly interesting nucleophiles could be carbon based ones such as indoles or heteroatom nucleophiles such as thiols.

A more challenging piece of work would be an intramolecular nitro-Mannich reaction that is redox neutral, using 1,5-hydride shift methodology.[68]

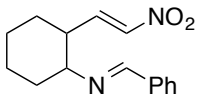
4.3 Increased Nitrostyrene Substrate Scope

As the substrate scope is somewhat limited at the moment, new methods to form nitrostyrene **199z** could be investigated. One method could be the conversion of electron poor 2-vinylanilines to the corresponding azide. Conversion of electron poor anilines such as *p*-cyanoaniline **229j** to the azide **302** and then an aza-Wittig reaction may lead to facile formation of imine **303**, which could then be nitrated to the desired nitrostyrene **199z** (Scheme 114).



Scheme 114: Aza-Wittig strategy to electron poor nitrostyrenes.

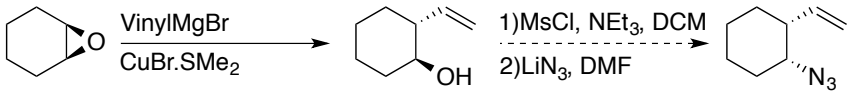
Another unexplored area of the intramolecular nitro-Mannich reaction is removing or replacing the phenyl backbone. One route of research is using a cyclohexyl scaffold such as nitrostyrene **304** (Figure 28).



304

Figure 28: Cyclohexyl nitrostyrene-imine **304**.

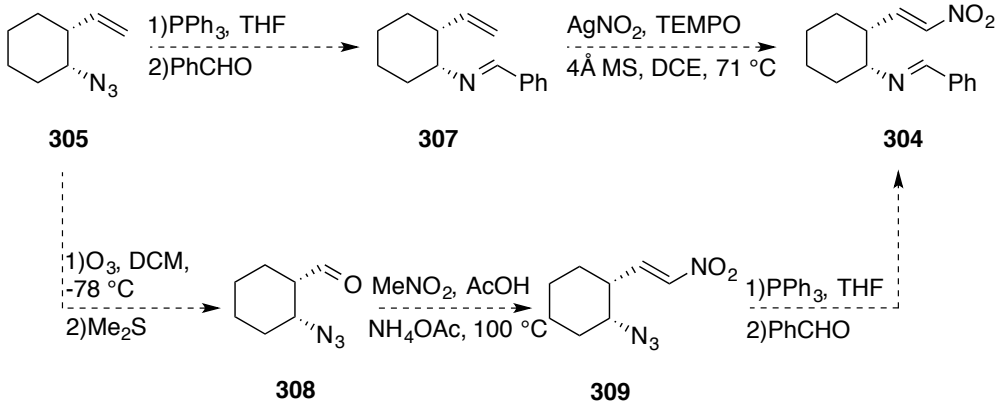
The synthesis of **304** can be disconnected back to azide **305** as the main intermediate. The azide **305** could be made by addition of vinylmagnesium bromide to cyclohexene oxide,[121] mesylation of alcohol **306** and displacement with LiN_3 to give our vinyl azide **305** (scheme 115).[122]



306 **305**

Scheme 115: Synthesis of 1-azido-2-vinyl-cyclohexane **305**.

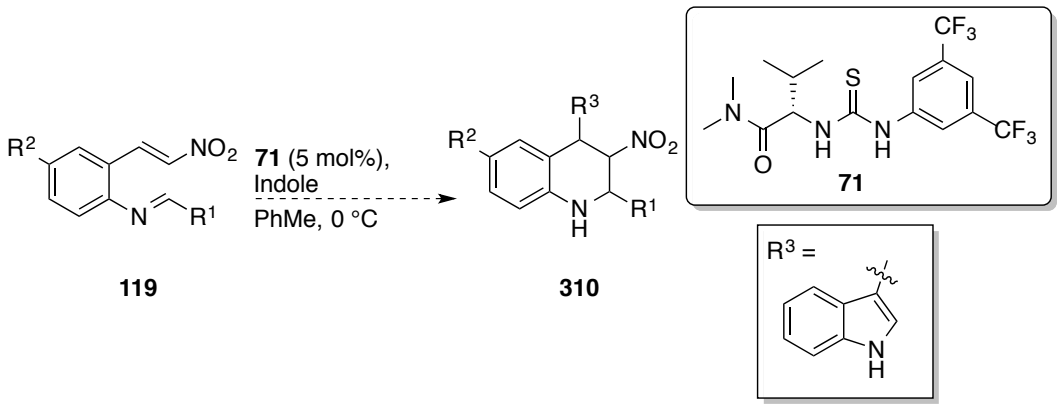
At this juncture one could carry on with an aza-Wittig strategy to give imine **307** and then attempt a radical nitration of the vinyl group to give nitrostyrene **304**. Alternatively one could ozonlyse the vinyl group to the aldehyde **308**, form nitroalkene **309** by a Henry reaction and then form the product **304** by an aza-Wittig reaction (Scheme 116).



Scheme 116: Different routes to tethered nitrostyrene-imine **304**.

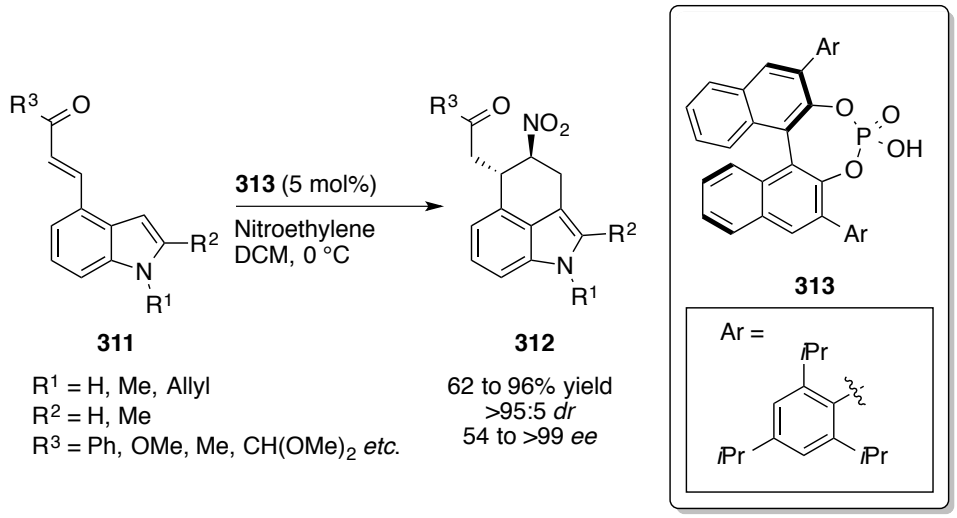
4.4 Expanding the Range of Nucleophiles

A tandem cyclisation triggered by the addition of indole to nitrostyrene **119** may be possible (Scheme 117).



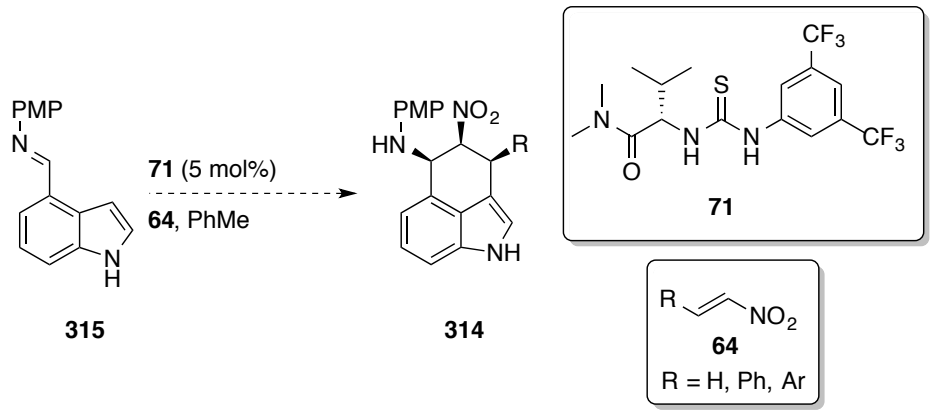
Scheme 117: Proposed addition of indole to nitrostyrene **119**.

A more interesting topic would be the use of the indole being both the nucleophile and the tethered imine. Bernardi *et al*. have described an interesting Friedel-Crafts/Michael/Michael cascade between nitroethylene and indole **311**. This result provided the *trans*-nitroalkane **312** in relatively high yields and enantioselectivity (Scheme 118).



Scheme 118: Asymmetric synthesis of Ergoline-like skeletons by Bernardi *et al*.

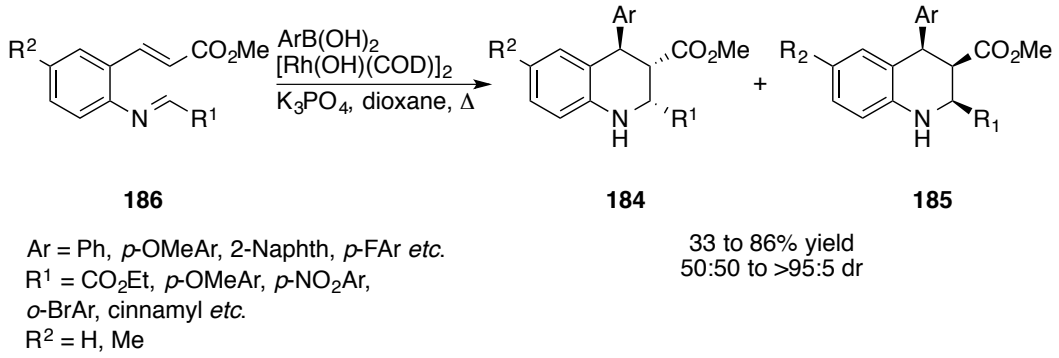
Combination of this methodology with the intramolecular nitro-Mannich reaction could afford the densely functionalised indole **314** in high yields and stereoselectivity (Scheme 119). If this chemistry is effective with nitroethylene, it could be expanded to nitrostyrenes to give three stereocentres in one-pot.



Scheme 119: Proposed thiourea catalysed Friedel-Crafts/Michael/nitro-Mannich cascade.

The addition of arylboronic acids to nitrostyrenes has been previously described, using a variety of ligands.[119] The nitronate intermediate has never been intercepted for a Henry reaction or a nitro-Mannich reaction. Related reactions have been reported, particularly the tandem

Michael/Mannich cyclisation to give the racemic densely functionalised tetrahydroquinoline, in relatively high yields and diastereoselectivity (Scheme 120).[74]



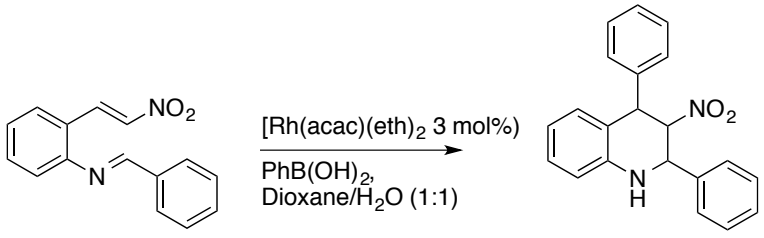
186 **184** **185**

Ar = Ph, *p*-OMeAr, 2-Naphth, *p*-FAr *etc.*
R^1 = CO_2Et, *p*-OMeAr, *p*-NO_2Ar,
o-BrAr, cinnamyl *etc.*
R^2 = H, Me

33 to 86% yield
50:50 to >95:5 dr

Scheme 120: Previous cyclisation of α,β-unsaturated ester-imine **186**.

A tandem rhodium catalyzed asymmetric conjugate addition/nitro-Mannich cyclisation has been investigated briefly (in collaboration with a visiting student Matus Diveky). Addition of the arylboronic acid appeared to give a 1:1 mixture of diastereomers by ^{1}H NMR when 3 mol% [Rh(acac)$(eth)_2$] was used as the catalyst (Scheme 121). This result shows a proof of principle that a rhodium catalyzed nitro-Mannich reaction is possible; further work is required to make this reaction diastereoselective before the absolute stereochemistry can be controlled.



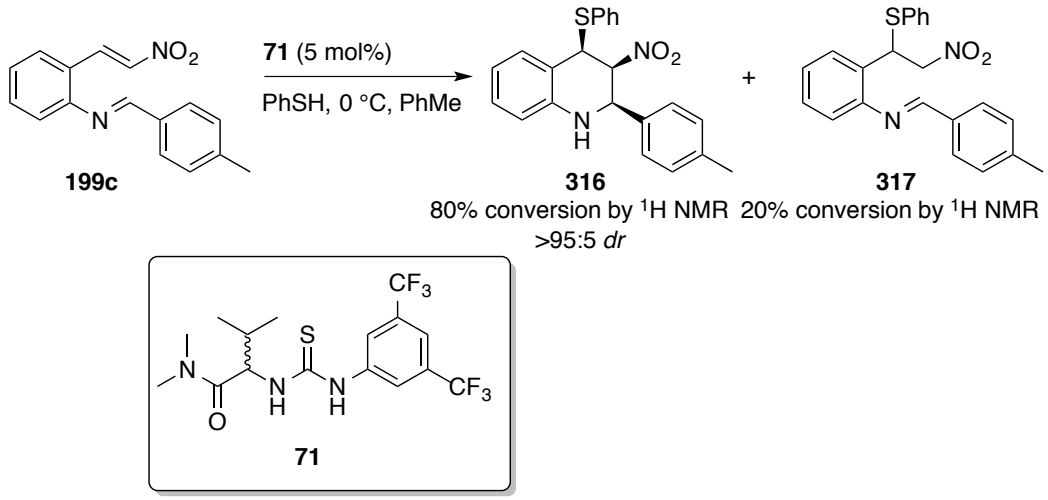
199a **296**

90% yield
1:1 *dr*

Scheme 121: Synthesis of densely functionalised tetrahydroquinoline **296**.

As there have been reports of thio-Michael/nitro-Mannich reactions, it could be possible to try the cyclisation of **199** to tetrahydroquinoline **316**

by addition of a thiol nucleophile. A preliminary experiment using thiophenol as the nucleophile was investigated. Addition of thiophenol to nitrostyrene **199c** with 5 mol% catalyst **71** provided a mixture of products and complete consumption of the starting material after 4 h. The reaction was monitored by ^{1}H NMR and TLC and the products were assigned as the tetrahydroquinoline **316** and nitroalkane **317** (Scheme 122), the stereochemistry was tentatively assigned as the *cis*,*cis* diastereomer by analysis of the ^{3}J coupling constants as previously described.

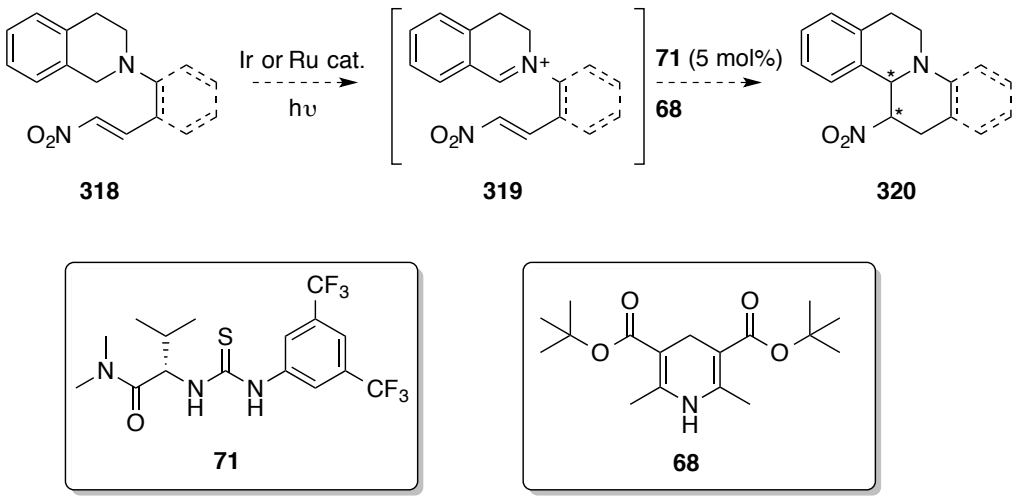


Scheme 122: Attempted Michael/nitro-Mannich reaction triggered by thiophenol.

This promising result may mean that a thio-Michael/nitro-Mannich cascade cyclisation is feasible and diastereoselective. The absolute stereochemistry may be controlled by the same catalyst as used previously or the thiourea may need modification.

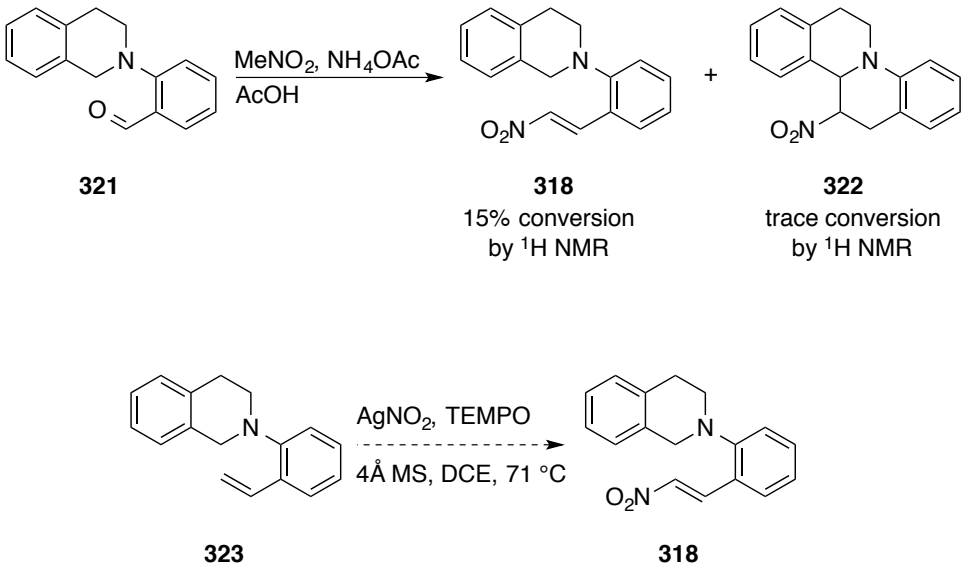
4.5 Redox-Neutral Tandem Nitro-Mannich Reactions

Other intramolecular cyclisations might be possible; tethering a nitrostyrene onto a tetrahydroisoquinoline such as **318** may form the iminium **319** with a catalyst and then the cyclised product **320** in the presence of **68** and **71** (Scheme 122).



Scheme 122: Proposed use of tethered nitrostyrene **318**.

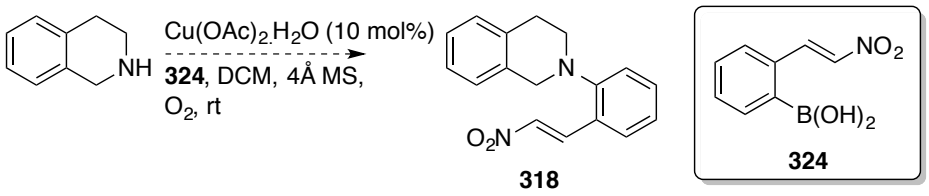
Synthesis of tethered nitrostyrene **318** could be made from the literature aldehyde **321** by a Henry-reaction (Scheme 123). When this reaction was attempted it appeared to give some conversion to the desired product, but also some overreaction to the cyclised product. Another potential disconnection would be the nitration of the styrene **323**, but TEMPO may oxidize the tetrahydroisoquinoline **318** in conjunction with a metal salt.[123]



Scheme 123: Synthesis of tethered nitrostyrene **318**.

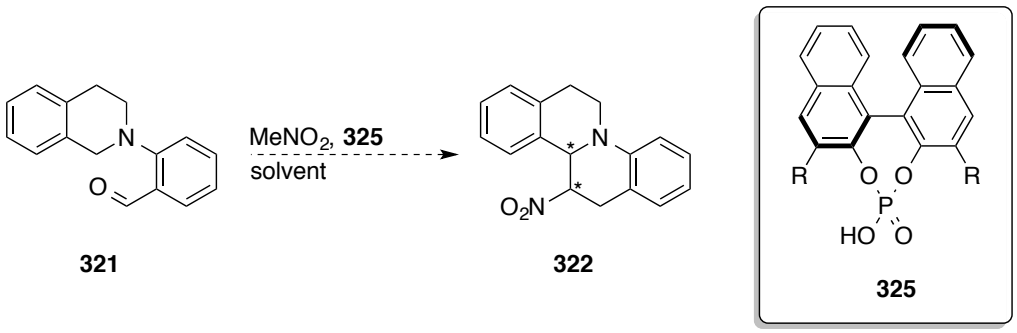
An Evans-Chan-Lam coupling may furnish the desired nitrostyrene **318** (Scheme 124). It has been found that tetrahydroquinoisoquinolines are

tolerant to the reaction conditions, without oxidation to the iminium.[124] The nitrostyrene **318** could then be used in the reaction as previously described.



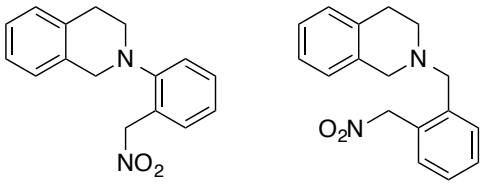
Scheme 124: Proposed Evans-Chan-Lam route to nitrostyrene **318**.

Drawing inspiration from Jordis *et al*. addition of nitromethane and use of a chiral phosphoric acid catalyst **325** may lead to a one-pot nitrostyrene formation/1,5-hydrideshift/nitro-Mannich reaction, with complete stereocontrol (Scheme 125).[68]



Scheme 125: One-pot tandem nitrostyrene formation/1,5-hydride shift/nitro-Mannich reaction.

There are other substrates that could be used for an iminium formation/nitro-Mannich reaction. The tetrahydroisoquinolines **326** and **327** may be used and their synthesis could be less synthetically challenging (Figure 26).[125]



326 **327**

Figure 26: Other interesting substrates for a tandem iminium formation/nitro-Mannich reaction.

5.0 Experimental

5.1 General Experimental Details

For all non-aqueous chemistry, glassware was flamed dried *in vacuo* and reactions were carried out under an inert (N_2 or Ar) atmosphere. Thin layer chromatography was performed on Polygram SilG/UV silica gel plates and visualization was performed using UV (254 nm), ninhydrin, Hannesian's stain, PMA or $KMnO_4$ solution. Flash chromatography was performed using Gedran silica gel 60, 40-63 μm. Removal of solvents *in vacuo* was achieved using the house vacuum and Büchi rotary evaporator.

5.2 Purification of Solvents and Reagents

Commercial solvents and reagents were used as supplied or purified by literature procedures. Dry solvents Et_2O, THF, DCM, toluene and hexanes were obtained from a solvents tower, where the degassed solvent ws passed through two columns of activated alumina and a 7 micron filter under 4 bar pressure. Butyl lithiums were titrated using either *N*-benzylbenzamide or diphenylacetic acid as an indicator.

Ligand **131**, nitrostyrene **222**, racemic-thiourea **71** and Imines **243** were previously synthesised within the group and were used without further purification.

2-Aminophenethyl alcohol **232** was made by the literature procedure from 2-nitrophenylacetic acid or purchased from Sigma-Aldrich.[126]

Racemic tetrahydroquinolines **175** for HPLC analysis were made using racemic thiourea **71** and had identical NMR data.

2-iodo-4-nitroaniline **235g**[127], 4-amino-3-iodobenzonitrile **235j**[128] and 4-fluoro-2-iodoaniline **235h**[129] were made by the literature procedures.

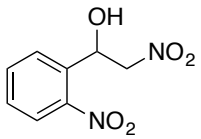
5.3 Characterisation

Melting points are reported uncorrected using a Reichert Melting Point Apparatus. All ^{1}H and ^{13}C NMR data were recorded using a Bruker ADVANCE III 400 MHz and Bruker ADVANCE III 600 MHz machines at 400 and 600 MHz for ^{1}H NMR and 100 and 125 MHz for ^{13}C. ^{19}F NMR data were recorded on a Bruker AMX 300 MHz machine at 282 MHz. All data were manipulated using ACD Labs Academic Edition or MestReNova (version 9.0). All chemical shifts (δ) are reported in parts per million (ppm), relative to residual solvent peaks δ = 7.26 for ^{1}H NMR and δ = 77.1 for ^{13}C NMR. Multiplicities for signals are denoted as s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, p = pentet, m = multiplet and br = broad, app = apparent. Coupling constants (*J*) are reported in Hertz (Hz). ^{13}C multiplicities were assigned using DEPT. To aid assignment HMQC, HMBC and NOE were used as appropriate. Mass spectroscopy data were collected on Thermo Finnigan Mat900xp (EI/CI). Infrared data was collected using Perkin-Elmer 100 FTIR spectrometer as a thin film. Elemental analysis was performed on an Exeter Analytic Inc. EA440 horizontal load analyser. Optical rotations were obtained using a Perkin-Elmer 343 model polarimeter.

5.4 Experimental Procedures

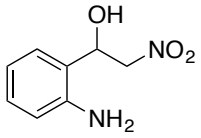
5.5 Nitroalcohol Synthesis

2-Nitro-1-(2-nitrophenyl)ethan-1-ol **210**



To 2-nitrobenzaldehyde (15 g, 99.3 mmol) and imidazole (1.68 g, 24.8 mmol) was added $MeNO_2$ (15.9 mL, 29.7 mmol) and H_2O (159 mL) and the mixture was stirred for 3 h. The reaction mixture was extracted with Et_2O (3 x 100 mL), the combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give nitro alcohol **210** as a brown oil and on standing a tan solid (17.95 g, 99%); mp 55-57 °C (lit. 60-61 °C[87]); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.03 (1H, d, *J* = 8.3 Hz, Ar*H*), 7.93 (1H, d, *J* = 7.9 Hz, ArH), 7.73 (1H, t, *J* = 7.5 Hz, Ar*H*), 7.53 (1H, t, *J* = 7.5 Hz, Ar*H*), 6.00 (1H, dd, *J* = 9.0, 2.3 Hz, C*H*OH), 4.83 (1H, dd, *J* = 13.6, 2.3 Hz, CH*H*NO_2), 4.54 (1H, dd, *J* = 13.6, 9.4 Hz, C*H*HNO_2), 4.32 (1H, br. s, O*H*).
Data consistent with literature.[87]

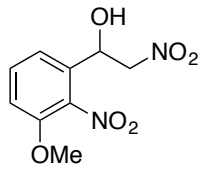
1-(2-Aminophenyl)-2-nitroethan-1-ol **203**



To a suspension of nitroalcohol **210** (4.98 g, 23.5 mmol) in DCM (35 mL) and EtOAc (35 mL) was added Pd/C (2.49 g, 10% wt on carbon, 10 mol%) and Pearlman's catalyst (823 mg, 20% wt on carbon, 5 mol%). The flask was triple evacuated/N_2 filled and then tripled evacuated/H_2 filled. The reaction mixture was stirred under a H_2 balloon for 5 h then tripled evacuated/N_2 filled. The reaction mixture was filtered through a pad of Celite, washed with DCM (3 x 20 mL) and concentrated *in vacuo* to give the crude aniline **203** as a red oil. Purification by recrystallisation

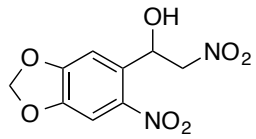
($CHCl_3$) afforded arylamine **203** as white crystals (3.29 g, 77%); mp 90-91 °C; R_f = 0.43 (2% MeOH/DCM); IR ν_{max} (neat) 3356 (O-H), 1610 (N-H), 1544 (N-O) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.15 (1H, dd, *J* = 7.5, 1.0 Hz, Ar*H*), 7.01 (1H, td, *J* = 7.3, 1.5 Hz, Ar*H*), 6.68 (1H, d, *J* = 8.0 Hz, Ar*H*), 6.58 (1H, td, *J* = 7.5, 1.0 Hz, Ar*H*), 6.08 (1H, d, *J* = 4.5 Hz, O*H*), 5.31 (1H, app. dt, *J* = 9.8, 4.0 Hz, C*H*OH), 5.07 (2H, br. s, NH_2), 4.76 (1H, dd, *J* = 9.8, 3.5 Hz, CH*H*NO_2), 4.58 (1H, dd, *J* = 12.4, 9.9 Hz, C*H*HNO_2); ^{13}C NMR (DMSO-d_6, 151 MHz) δ 145.82 (A*rC*), 128.54 (Ar*C*H), 127.06 (Ar*C*H), 123.16 (ArC), 116.53 (Ar*C*H), 115.93 (Ar*C*H), 79.42 (CH_2NO_2), 68.08 (*C*HOH); m/z (EI) 182 (100%, $M^{+\cdot}$); HRMS $C_8H_{10}N_2O_3$ calcd. 182.0686, found 182.0685; Anal. calcd. for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.48; found: C, 52.97; H, 5.42; N, 15.12%.

1-(3-Methoxy-2-nitrophenyl)-2-nitroethan-1-ol **216**



A suspension of 3-methoxy-2-nitrobenzaldehyde (872 mg, 4.80 mmol) and imidazole (85.0 mg, 1.25 mmol) in $MeNO_2$ (800 µL) and H_2O (6 mL) was left to stir for 24 hours. The reaction mixture was added brine (40 mL), the product was extracted with DCM (3 x 20 mL), the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the pure nitroalcohol **216** as a brown solid (1.22 g, 100%); R_f = 0.30 (6:4 Et_2O:pet. Ether); mp 96-98 °C; 1H NMR (600 MHz, $CDCl_3$) δ 7.51 (1H, dd, *J* = 8.4, 7.9 Hz, Ar*H*), 7.24 (1H, ddd, *J* = 7.9, 1.1, 0.6 Hz, Ar*H*), 7.07 (1H, dd, *J* = 8.5, 1.1 Hz, Ar*H*), 5.47 (1H, dd, *J* = 9.3, 2.9 Hz, C*H*OH), 4.66 (1H, dd, *J* = 13.9, 2.9 Hz, C*H*HNO_2), 4.61 (1H, dd, *J* = 13.9, 9.3 Hz, CH*H*NO_2), 3.92 (3H, s, OCH_3), 2.87 (1H, br. s, O*H*).
Data in agreement with literature.[130]

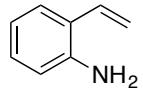
2-Nitro-1-(6-nitrobenzo[*d*][1,3]dioxol-5-yl)ethan-1-ol **217**



A suspension of 6-nitropiperonal (1.92 g, 10.0 mmol) and imidazole (170 mg, 2.50 mmol) in $MeNO_2$ (1.62 mL, 30.0 mmol) and H_2O (12 mL) was left to stir for 24 h. The reaction mixture was added brine (50 mL), the product was extracted with DCM (3 x 25 mL), the combined organic extracts were washed with brine (75 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude nitroalcohol **217** as a brown solid. Purification by column chromatography (1:1 pet. Ether:Et_2O) gave the pure nitroalcohol **217** as a yellow solid (1.13 g, 44%); R_f = 0.15 (6:4 pet. Ether:Et_2O); IR ν_{max} (neat) 1558 (N-O), 1506 (N-O), 1375 (N-O); 1314 (N-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.59 (1H, s, Ar*H*), 7.36 (1H, d, *J* = 0.6 Hz, Ar*H*), 6.18 (1H, d, *J* = 1.2 Hz, OC*H*HO), 6.16 (1H, d, *J* = 1.2 Hz, OCH*H*O), 6.07 (1H, dddd, *J* = 8.9, 4.2, 2.3, 0.6 Hz, C*H*OH), 4.84 (1H, ddd, *J* = 13.9, 2.3, 0.5 Hz, C*H*HNO_2), 4.48 (1H, dd, *J* = 13.8, 9.0 Hz, CH*H*NO_2), 3.15 – 3.13 (1H, m, O*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 153.2 (Ar*C*), 148.3 (Ar*C*), 141.3 (Ar*C*), 131.5 (Ar*C*), 107.4 (Ar*C*H), 105.8 (Ar*C*H), 103.6 (O*C*H_2O), 80.0 (*C*H_2NO_2), 67.0 (*C*HOH); m/z (EI) 256 (100%, $M^{+\cdot}$); HRMS $C_8H_8N_2O_7$ calcd. 256.0326, found 256.0325.

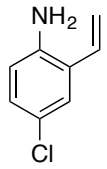
5.6 Aminostyrene Synthesis

2-Vinylaniline **229a**



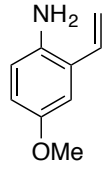
A mixture of 2-aminophenethylalcohol **232** (3.61 g, 26.0 mmol) and KOH (1.46 g, 26.0 mmol) was heated at 180 °C in a distillation apparatus under vacuum. Purification by vacuum distillation (200 °C, 1 mbar) gave the pure 2-aminostyrene **299a** as a colourless oil (2.46 g, 80%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (1H, dd, *J* = 7.7, 1.6 Hz, Ar*H*), 7.10 (1H, td, *J* = 7.6, 1.6 Hz, Ar*H*), 6.86 – 6.62 (3H, m, C*H*), 5.64 (1H, dd, *J* = 17.5, 1.5 Hz, C*H*), 5.33 (1H, dd, *J* = 11.1, 1.5 Hz, C*H*), 3.40 (2H, br. s, NH_2).
Data consistent with literature.[131]

4-Chloro-2-vinylaniline **229b**



A solution of 2-iodoaniline **235b** (759 mg, 3.00 mmol) and $Pd(OAc)_2$ (35 mg, 0.15 mmol, 5 mol%) in MeOH (15 mL) was stirred for 5 min, then potassium vinyltrifluoroborate (402 mg, 3.00 mmol) and K_2CO_3 (1.24 g, 9.00 mmol) were added and the reaction was left to stir for 24 h at 65 °C. The reaction mixture was diluted with brine (75 mL), the product was extracted with EtOAc (3 x 50 mL), the combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude styrene **229b** as a brown oil. Purification by column chromatography (9:1 Hexanes:EtOAc) gave the pure styrene **229b** as a brown oil (253 mg, 55%); R_f = 0.16 (pet. Ether:EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27 (1H, d, *J* = 2.5 Hz, Ar*H*), 7.06 (1H, dd, *J* = 8.5, 2.5 Hz, Ar*H*), 6.71 (1H, dd, *J* = 17.3, 11.0 Hz, C*H*), 6.63 (1H, d, *J* = 8.5 Hz, ArH), 5.66 (1H, dd, J = 17.4, 1.1 Hz, CH*H*), 5.38 (1H, dd, *J* = 11.0, 1.3 Hz, C*H*H), 3.66 (2H, br. s., NH_2).
Data consistent with literature.[132]

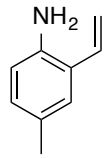
4-Methoxy-2-vinylaniline **229c**



A solution of 2-iodoaniline **235c** (249 mg, 1.00 mmol) and $Pd(OAc)_2$ (11.0 mg, 0.15 mmol, 5 mol%) in MeOH (4 mL) was stirred for 5 min, then potassium vinyltrifluoroborate (402 mg, 3.00 mmol) and K_2CO_3 (413 mg, 3.00 mmol) were added and the reaction was left to stir for 24 hours at 65 °C. The reaction mixture was diluted with brine (50 mL), the product was extracted with EtOAc (3 x 30 mL), the combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to

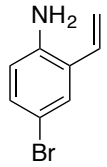
give the crude styrene **229c** as a brown oil. Purification by column chromatography (9:1 Hexanes:EtOAc) gave pure styrene **229c** as a brown oil (66 mg, 44%); R_f = 0.27 (9:1 pet. Ether:EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.88 (1H, d, *J* = 2.9 Hz, Ar*H*), 6.78 (1H, dd, *J* = 17.4, 11.0 Hz, C*H*), 6.71 (1H, dd, *J* = 8.6, 2.9 Hz, Ar*H*), 6.64 (1H, d, *J* = 8.6 Hz, Ar*H*), 5.64 (1H, dd, *J* = 17.4, 1.4 Hz, CH*H*), 5.32 (1H, dd, *J* = 11.0, 1.4 Hz, C*H*H), 3.77 (3H, s, OCH_3), 3.65 (2H, br. s., NH_2).
Data consistent with literature.[133]

4-Methyl-2-vinylaniline **229d**



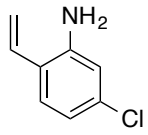
A suspension of 2-iodoaniline **235d** (1.40 g, 6.00 mmol), K_2CO_3 (2.48 g, 18.0 mmol), potassium trifluoroborate (798 mg, 6.00 mmol) and $Pd(OAc)_2$ (67.0 mg, 0.30 mmol, 5 mol%) in MeOH (12 mL) was stirred at 65 °C for 18 hours. The reaction mixture was diluted with brine (90 mL), the product was extracted with DCM (3 x 45 mL), the combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude styrene **229d** as a brown wax. Purification by column chromatography (9:1 Hexanes:EtOAc) gave pure styrene **229d** as a golden oil (330 mg, 41%); R_f = 0.20 (9:1 pet. Ether:EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.12 (1H, s, Ar*H*), 6.92 (1H, dd, *J* = 8.0, 1.9 Hz, Ar*H*), 6.78 (1H, dd, *J* = 17.4, 11.1 Hz, C*H*), 6.62 (1H, d, *J* = 8.0 Hz, Ar*H*), 5.63 (1H, dd, *J* = 17.4, 1.5 Hz, CH*H*), 5.31 (1H, dd, *J* = 11.1, 1.5 Hz, C*H*H), 3.69 (2H, br. s., NH_2), 2.26 (3H, s, CH_3),
Data consistent with literature.[134]

4-Bromo-2-vinylaniline **229e**



To a suspension of 4-bromo-2-iodoaniline **235e** (2.98 g, 10.0 mmol), potassium vinyltrifluoroborate (1.34 g, 10.0 mmol), K_2CO_3 (1.66 g, 12.0 mmol) and $Pd(PPh_3)_4$ (1.16 g, 10 mol%, 1.00 mmol) in DME (30 mL) was added H_2O (10 mL) and the reaction was left to stir for 18 h at 85 °C. The reaction mixture was diluted with brine (100 mL), the product was extracted with EtOAc (3 x 50 mL), the combined organic extracts dried (Na_2SO_4) and concentrated *in vacuo* to give the crude styrene **229e** as a brown oil. Purification by column chromatography (9:1 pet. Ether:EtOAc) gave the pure styrene **229e** as a low melting brown solid (980 mg, 49%); R_f = 0.23 (9:1 pet. Ether:EtOAc); IR ν_{max} (neat) 3413 (N-H), 1618 (C=C) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.38 (1H, d, *J* = 2.3 Hz, Ar*H*), 7.16 (1H, dd, *J* = 8.5, 2.3 Hz, Ar*H*), 6.67 (1H, dd, *J* = 17.4, 11.0 Hz, C*H*), 6.56 (1H, d, *J* = 8.5 Hz, Ar*H*), 5.63 (1H, dd, *J* = 17.4, 1.2 Hz, C*H*H), 5.35 (1H, dd, *J* = 11.0, 1.2 Hz, C*H*H), 3.75 (2H, br. s, NH_2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.3 (Ar*C*), 131.6 (*C*H), 131.4 (*C*H), 129.9 (*C*H), 126.3 (Ar*C*), 117.9 (*C*H), 117.3 (*C*H_2), 111.2 (Ar*C*); m/z (ESI+) 198 (100%, $M+H^+$); HRMS $C_8H_9N(^{79}Br)$ calcd. 197.9913, found 197.9911.

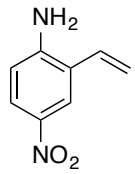
5-Chloro-2-vinylaniline **229f**



To a suspension of iodoaniline **235f** (1.52 g, 6.00 mmol), vinylboronic anhydride pyridine complex (1.44 g, 6.00 mmol), K_2CO_3 (993 mg, 7.20 mmol) and $Pd(PPh_3)_4$ (36.0 mg, 0.30 mmol, 5 mol%) in DME (24 mL) was added H_2O (7.8 mL) and the reaction was left to stir for 72 h at 65 °C. The reaction mixture was diluted with brine (150 mL), the product was

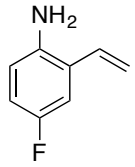
extracted with DCM (3 x 100 mL), the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give the crude styrene **229f** as a red oil. Purification by column chromatography (9:1 Hexanes:EtOAc) gave the pure styrene **229f** as a yellow oil (430 mg, 47%); R_f = 0.28 (6:4 pet.Ether:Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (1H, d, *J* = 8.4 Hz, Ar*H*), 7.00 (1H, dd, *J* = 17.5, 11.0 Hz, C*H*), 6.67 (1H, d, *J* = 2.4 Hz, Ar*H*), 6.55 (1H, dd, *J* = 8.5, 2.4 Hz, Ar*H*), 5.56 (1H, dd, *J* = 17.5, 1.2 Hz, C*H*H), 5.18 (1H, dd, *J* = 11.0, 1.2 Hz, CH*H*), 3.74 (2H, s, NH_2).
Data in agreement with literature.[135]

4-Nitro-2-vinylaniline **229g**



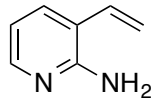
To a solution of iodoaniline **235g** (1.74 g, 8.00 mmol), $Pd(OAc)_2$ (90.0 mg, 0.40 mmol, 5 mol%), $P(furyl)_3$ (186 mg, 0.80 mmol, 10 mol%) in PhMe (30 mL) was added vinyltributyltin (2.80 mL, 9.60 mmol) and stirred at 100 °C for 24 hours. The reaction mixture was diluted with brine (150 mL), the product was extracted with EtOAc (3 x 75 mL), the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give the crude styrene **229g** as a black oily solid. Purification by column chromatography (2 x 7:3 Hexanes:EtOAc) gave the pure styrene **229g** as a red oil (220 mg, 17%); R_f = 0.46 (1:1 pet. Ether:EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.18 (1H, d, *J* = 2.5 Hz, Ar*H*), 7.99 (1H, dd, *J* = 8.9, 2.6 Hz, ArH), 6.73 – 6.62 (2H, m, Ar*H* & C*H*), 5.76 (1H, dd, *J* = 17.3, 1.0 Hz, C*H*H), 5.49 (1H, dd, *J* = 11.0, 1.0 Hz, CH*H*), 4.46 (2H, s, NH_2); ^{13}C NMR (151 MHz, $CDCl_3$) δ 149.7 (Ar*C*), 139.5 (Ar*C*H), 130.8 (*C*H), 125.2 (Ar*C*), 124.2 (Ar*C*H), 123.0 (Ar*C*H), 119.1 (*C*H_2), 114.6 (Ar*C*).
Data in agreement with literature.[134]

4-Fluoro-2-vinylaniline **229h**



To a solution of iodoaniline **235h** (1.42 g, 6.00 mmol), K_2CO_3 (6.10 g, 18.0 mmol) and $Pd(OAc)_2$ (68 mg, 0.30 mmol, 5 mol%) in MeOH (15 mL) was added potassium vinyltrifluoroborate (804 mg, 6.00 mmol) and the reaction was left to stir for 5 h at 65 °C. The reaction mixture was diluted with brine (100 ml), the product was extracted with EtOAc (3 x 40 mL), the combined organic extracts dried ($MgSO_4$) and concentrated *in vacuo* to give the crude styrene **229h** as a brown oil. Purification by column chromatography (8:2 pet. Ether:EtOAc) gave the pure styrene **229h** as a brown oil (587 mg, 71%); R_f = 0.33 (8:2 pet. Ether:EtOAc); IR ν_{max} (neat) 3446 (N-H), 3087 (=CH_2), 1492 (N-H), 1152 (C-F) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) 7.02 (1H, dd, *J* = 9.7, 2.9 Hz, Ar*H*), 6.81 (1H, td, *J* = 8.4, 2.9 Hz, Ar*H*), 6.73 (1H, dd, *J* = 17.3, 11.0 Hz, C*H*), 6.62 (1H, dd, *J* = 8.7, 4.9 Hz, Ar*H*), 5.64 (1H, dd, *J* = 17.4, 1.2 Hz, CH*H*), 5.38 (1H, dd, *J* = 11.0, 1.1 Hz, C*H*H), 3.62 (2H, br. s, NH_2); ^{13}C NMR ($CDCl_3$, 126 MHz) 156.7 (1C, d, *J* = 237.0 Hz, *C*F), 139.7 (Ar*C*), 131.9 (*C*H), 125.3 (1C, d, *J* = 6.7 Hz, Ar*C*), 117.2 (1C, d, *J* = 7.7 Hz, *C*H), 116.7 (*C*H_2), 115.3 (1C, d, *J* = 23.0 Hz, *C*H), 113.2 (1C, d, *J* = 22.1 Hz, *C*H); ^{19}F NMR ($CDCl_3$, 282 MHz) -126.34 (1F, s, Ar*F*); m/z (EI) 137 (100%, M^+),136 (55%, M^+-H), 107 (22%, M-NH_2CH_2); HRMS C_8H_8FN calcd. 137.0648, found 137.0647.

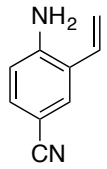
3-Vinylpyridin-2-amine **229i**



To a solution of 3-bromo-2-aminopyridine (688 mg, 4.00 mmol) and $Pd(PPh_3)_4$ (231 mg, 0.20 mmol, 5 mol%) in MeOH (10 mL) was left to stir for 10 min, potassium vinyltrifluoroborate (536 mg, 4.00 mmol) and K_2CO_3 (1.66 g, 12.0 mmol) were left to stir for 24 h at 90 °C. The reaction mixture was diluted with brine (100 mL), the product was extracted with EtOAc (3 x 50 mL), the combined organic extracts washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude styrene **229i** as a brown oil. Purification by column chromatography (6:4 to 4:6 Hexanes:EtOAc) gave the pure styrene **229i** as a yellow oil (288 mg, 60%); R_f = 0.08 (7:3 pet.Ether:EtOAc); IR ν_{max} (neat) 3471 (N-H), 3085 (CH_2), 2999 (CH_2) 1626 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 8.00 (1H, dd, *J* = 7.2, 5.0 Hz, Ar*H*), 7.50 (1H, ddd, *J* = 7.4, 1.8, 0.6 Hz, Ar*H*), 6.68 (1H, dd, *J* = 7.2, 5.0 Hz, Ar*H*), 6.63 (1H, dd, *J* = 17.4, 11.0 Hz, C*H*), 5.65 (1H, dd, 17.3, 1.1 Hz, CH*H*), 5.38 (1H, dd, *J* = 11.1, 1.1 Hz, C*H*H), 4.64 (2H, br. s, $ArNH_2$); ^{13}C NMR (CDCl3, 151 MHz) 155.6 (*C*NH_2), 147.2 (*C*H), 135.0 (*C*H), 131.6 (*C*H), 118.5 (Ar*C*), 117.2 (*C*H_2), 114.6 (*C*H); m/z (EI) 119 (100%, M^+-H), 120 (44%, M^+); HRMS $C_7H_8N_2$ calcd. 120.0688, found 120.0680.

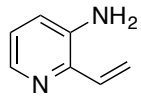
Data in agreement with literature.[136]

4-Amino-3-vinylbenzonitrile **229j**



A solution of iodoaniline **235j** (1.46 g, 6.00 mmol), K_2CO_3 (993 mg, 7.20 mmol) and $Pd(PPh_3)_4$ (36 mg, 0.30 mmol, 5 mol%) in DME (24 mL) was left to stir for 10 min. To the reaction mixture was added O'Shea's reagent (1.44 g, 6.00 mmol) and H_2O (7.80 mL) and the reaction was left to stir for 6 h at 95 °C. The reaction mixture was diluted with brine (100 mL), the product was extracted with EtOAc (3 x 75 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give the crude styrene **229j** as a brown oil. Purification by column chromatography (8:2 Hexanes:EtOAc) gave the pure styrene **229j** as a low melting cream solid (420 mg, 49%); R_f = 0.25 (8:2 pet. Ether:EtOAc); IR ν_{max} (neat) 3460 (N-H), 3364 (N-H), 2212 (CN) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52 (1H, s, Ar*H*), 7.39 – 7.30 (1H, m, Ar*H*), 6.74 – 6.53 (2H, m, C*H*), 5.66 (1H, d, *J* = 17.3 Hz, C*H*), 5.44 (1H, d, *J* = 11.0 Hz, C*H*), 4.29 (2H, s, NH_2); ^{13}C NMR (151 MHz, $CDCl_3$) δ 147.6 (*C*N), 132.7 (*C*H), 131.9 (*C*H), 131.0 (*C*H), 124.0 (Ar*C*), 120.1 (Ar*C*), 118.5 (CH_2), 115.6 (*C*H), 100.9 (Ar*C*); m/z (EI) 137 (88%, $M+H^+$),HRMS $C_9H_9N_2$ calcd. 145.0766, found 145.0764.

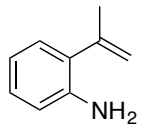
2-Bromopyridin-3-amine **229k**



To a mixture of bromopyridine (1.00 g, 5.78 mmol), $Pd(PPh_3)_4$ (668 mg, 0.58 mmol, 10 mol%), K_2CO_3 (966 mg, 7.23 mmol) and O'Sheas reagent (1.67 g, 6.94 mmol) was added DME (40 mL) then H_2O (15 mL) and then heated to 85 °C for 4 h. The reaction was diluted with brine (20 mL), the product was extracted with EtOAc (3 x 50 mL), the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give the crude

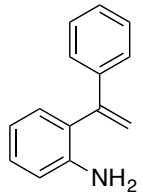
vinylpyridine **229k** as an orange oil. Purification by column chromatography (1:1 Hexanes:EtOAc) gave the pure vinylpyridine **229k** as a yellow oil (570 mg, 82%); R_f = 0.23 (1:1 pet.Ether:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (1H, dd, *J* = 4.3, 1.8 Hz, Ar*H*), 7.05 – 7.00 (2H, m, Ar*H*), 6.86 (1H, dd, *J* = 17.2, 11.1 Hz, C*H*), 6.26 (1H, dd, *J* = 17.2, 1.7 Hz, C*H*), 5.56 (1H, dd, *J* = 11.1, 1.7 Hz, C*H*), 3.81 (2H, br. s, NH_2).
Data in agreement with literature.[136]

2-(Prop-1-en-2-yl)aniline **238a**



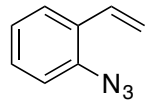
A solution of methyltriphenylphosphonium bromide (5.36 g, 15.0 mmol) in THF (100 mL) was cooled to 0 °C, KO*t*Bu (1.68 g, 15.0 mmol) was added portion wise and the reaction was left to stir for 30 min at rt. To the reaction mixture was added 2-aminoacetophenone (1.35 g, 10.0 mmol) dropwise and left to stir for 18 h at rt. The reaction mixture was added sat. NH_4Cl (150 mL), the product was extracted with EtOAc (3 x 75 mL), the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give the crude amine **238a** as a brown oil. Purification by column chromatography (Hexanes:EtOAc) gave the pure aniline **238a** as a brown oil (1.25 g, 65%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.11 – 6.97 (m, 2H, Ar*H*), 6.77 – 6.67 (2H, m, Ar*H*), 5.37 – 5.00 (2H, m, CH), 3.84 (2H, br. s, NH_2), 2.08 (3H, t, *J* = 1.2 Hz, CH_3).
Data in agreement with literature.[137]

2-(1-Phenylvinyl)aniline **238b**



A suspension of methyltriphenylphosphonium bromide (6.79 g, 19.0 mmol) in THF (50 mL) was cooled to 0 °C over 30 min. The reaction mixture was added KO*t*Bu (2.13 g, 19.0 mmol) portion wise and left to stir for 1 h. The reaction mixture was then added 2-aminobenzophenone (2.50 g, 12.7 mmol) in THF (30 mL) dropwise and the reaction was left to stir for 18 hr. The reaction mixture was added sat. NH_4Cl (100 mL), the product was extracted with EtOAc (3 x 75 mL), the combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give the crude styrene **238b** as a yellow gum. Purification by column chromatography (9:1 Hexanes:EtOAc) gave the pure styrene **238b** as a yellow solid (2.35 g, 95%); R_f = 0.39 (9:1 pet.Ether:EtOAc); mp 80-82 °C (lit.[136] 80-81 °C); 1H NMR ($CDCl_3$, 300 MHz) δ 7.42 – 7.29 (5H, m, ArH), 7.21-7.09 (2H, m, Ar*H*), 6.81 (1H, td, *J* = 7.4, 1.2 Hz, Ar*H*), 6.72 (1H, dd, *J* = 8.0, 1.2 Hz, Ar*H*), 5.81 (1H, d, *J* = 1.5 Hz, C*H*H), 5.37 (1H, d, *J* = 1.5 Hz, CH*H*), 3.53 (2H, br. s, NH_2).
Data consistent with literature.[138]

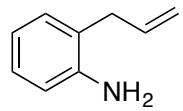
1-Azido-2-vinylbenzene **242**



A solution of 2-vinylaniline **229a** (238 mg, 2.00 mmol) in MeCN (7 mL) was cooled to 0 °C over 15 min. To the reaction mixture was added *t*BuONO (358 µL, 3.00 mmol), then added $TMSN_3$ (394 µL, 3.00 mmol) and the reaction was stirred for 3 h. The reaction mixture was concentrated *in vacuo* to give the crude styrene **242** as a brown oil. Purification by column chromatography (98:2 Hexanes:Et_2O) gave the pure styrene **242** as a yellow oil (261 mg, 90%); R_f = 0.68 (9:1 pet.Ether:EtOAc); IR ν_{max} (neat) 2104 (NN), 1626 (C=C) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.52 (1H, dd, *J* = 7.8, 1.5 Hz, Ar*H*), 7.30 (1H, td, *J* = 7.7, 1.6 Hz, Ar*H*), 7.17 – 7.10 (2H, m, Ar*H*), 6.95 (1H, dd, *J* = 17.6, 11.1 Hz, C*H*), 5.74 (1H, dd, *J* = 17.6, 1.2 Hz, CH*H*), 5.31 (1H, dd, *J* = 11.1, 1.2 Hz, C*H*H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 137.3 (Ar*C*), 131.5 (Ar*C*H), 129.6 (Ar*C*), 129.1 (Ar*C*H), 126.7 (Ar*C*H), 125.0 (Ar*C*H), 118.6 (*C*H_2), 115.8 (*C*H); m/z (EI) 145 (100%, $M^{+\cdot}$); HRMS $C_7H_7N_3$ calcd. 145.0635, found 145.0636.

N.B. Compound polymerises slowly at -15 °C

2-Allylaniline **244**



To a solution of 2-iodoaniline (2.19 g, 10.0 mmol) and $Pd(PPh_3)_4$ (1.16 g, 1.00 mmol, 10 mol%) in PhMe (50 mL) was added allyl tributyltin (3.10 mL, 10.0 mmol) and the reaction was heated to 100 °C for 3 h. To the reaction mixture was added brine (100 mL), the product was extracted with EtOAc (3 x 40 ML), the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give the crude aniline **244** as a golden brown oil. Purification by column chromatography (95:5

pet.Ether:Et_2O, ~3 cm K_2CO_3 pre-column) gave the pure aniline **244** as a brown oil (1.33 g, 29%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 – 7.01 (2H, m, Ar*H*), 6.81 – 6.62 (2H, m, Ar*H*), 5.96 (1H, ddt, *J* = 16.6, 10.4, 6.2 Hz, C*H*), 5.19 – 4.95 (2H, m, C*H*), 3.78 (2H, br. s, NH_2), 3.32 (2H, dt, *J* = 6.2, 1.7 Hz, CH_2).

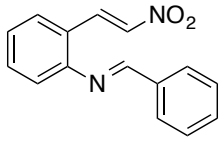
Data in agreement with literature.[91]

5.7 Nitrostyrene Synthesis

General procedure A

To a suspension of aminostyrene (2.00 mmol) in DCE (10 mL) was added aldehyde (2.00 mmol) and AcOH (6.00 mmol). The reaction mixture was left to stir for 48 h at room temperature. The solution was concentrated *in vacuo*. The residues were dissolved in DCE (6 mL) before $AgNO_2$ (6.00 mmol), 4Å molecular sieves (600 mg) and TEMPO (0.30 mmol) were added. The reaction was stirred for 2 h at 65 °C in air, filtered through a pad of Celite and concentrated *in vacuo* to give the crude nitrostyrene, which was purified by column chromatography (9:1 Hexanes:EtOAc).

(*E*)-*N*-(2-((*E*)-2-Nitrovinyl)phenyl)-1-phenylmethanimine **199a**



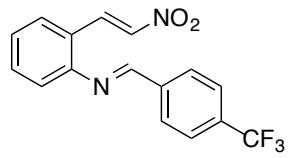
Prepared using general procedure **A**. Benzaldehyde (212 mg, 2.00 mmol) gave the crude nitrostyrene **199a** as a red solid. Purification by column chromatography (9:1 Hexanes:EtOAc) gave the crude nitrostyrene **199a** as a brown oil (489 mg, 97%); R_f = 0.25 (8:2 Hexane:Et_2O); IR ν_{max} (neat) 1623 (C=N), 1509 (N-O), 1332 (N-O), 964 (C-H) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.44 (1H, s, CHN), 8.44 (1H, d, *J* = 13.9 Hz, C*H*), 7.97 (2H, dd, *J* = 7.7, 1.6 Hz, Ar*H*), 7.75 (1H, d, *J* = 13.7 Hz, C*H*), 7.50 - 7.60 (5H, m, Ar*H*), 7.31 (1H, td, *J* = 7.6, 1.1 Hz, Ar*H*), 7.10 (1H, dd, *J* = 8.0, 0.9 Hz, Ar*H*); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 161.4 (*C*HN), 152.3 (Ar*C*), 138.5 (*C*H), 136.3 (*C*H), 135.6 (Ar*C*), 133.0 (Ar*C*H), 132.2 (Ar*C*H), 130.0 (Ar*C*H), 129.2 (Ar*C*H), 129.0 (Ar*C*H), 126.4 (Ar*C*H), 124.4 (Ar*C*), 119.1 (Ar*C*H); m/z (EI) 206 (100%, M^+-NO_2); HRMS $C_{15}H_{12}N_2O_2$ calcd. 252.0893, found 252.0895.

Alternative procedure:

To a solution of aryl amine **203** (500 mg, 2.74 mmol) in THF (7 mL) was added benzaldehyde (280 μL, 2.74 mmol) and the reaction was left to stir for 18 h. The reaction mixture was cooled to 0 °C over 10 min and TFAA

(318 μL, 2.25 mmol) added dropwise, then left to stir for 30 min at 0 °C. NEt_3 (940 μL, 6.75 mmol) was added dropwise and the reaction was left to stir for 30 min at 0 °C, then brought to RT over 10 min. The reaction mixture was concentrated *in vacuo* to give the crude imine **199a** as a brown oil. Purification by column chromatography (8:2 Hexanes:Et_2O) gave imine **199a** as a light brown oil (380 mg, 67%); Data same as above.

(*E*)-*N*-(2-((*E*)-2-Nitrovinyl)phenyl)-1-(4(trifluoromethyl)phenyl)methanimine **199b**



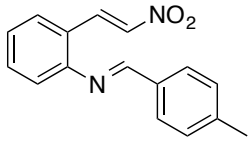
Prepared using general procedure **A.** *p*-Trifluoromethylbenzaldehyde (348 mg, 2.00 mmol) gave the crude nitrostyrene **199b** as a red wax. Purification by column chromatography (8:2 Hexanes:EtOAc) gave the pure nitrostyrene **199b** as a yellow solid (608 mg, 95%); mp 65-67 °C; R_f = 0.30 (8:2 pet. Ether:EtOAc); IR ν_{max} (neat) 1625 (C=N), 1505 (N-O), 1335 (N-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.49 (1H, s, C*H*N), 8.44 (1H, d, *J* = 13.7 Hz, C*H*), 8.07 (2H, d, *J* = 8.0 Hz, Ar*H*), 7.78 (2H, d, *J* = 8.1 Hz, Ar*H*), 7.68 (1H, d, *J* = 13.7 Hz, C*H*), 7.60 (1H, dd, *J* = 7.8, 1.4 Hz, Ar*H*), 7.54 (1H, td, *J* = 7.7, 1.4 Hz, Ar*H*), 7.35 (1H, td, *J* = 7.6, 1.1 Hz, Ar*H*), 7.12 (1H, dd, *J* = 8.0, 1.1 Hz, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.9 (*C*HN), 151.4 (Ar*C*), 138.6 (Ar*C*), 138.6 (*C*H), 138.5 (*C*H), 136.0 (Ar*C*H), 133.61 (1C, q, *J* = 32.5 Hz, Ar*C*), 133.2 (Ar*C*H), 129.8 (Ar*C*H), 129.4 (Ar*C*H), 127.1 (Ar*C*H), 126.1 (1C, q, *J* = 3.7 Hz, Ar*C*H), 124.8 (1C, q, *J* = J = 271.5 Hz, Ar*C*F_3), 119.0 (ArC); ^{19}F NMR (282 MHz, $CDCl_3$) δ -62.95 (3F, s, C*F*$_3$); m/z (CI) 321 (100%, $M+H^+$), 274 (60%, $M\text{-}NO_2^+$); HRMS $C_{16}H_{12}F_3N_2O_2$ calcd. 321.0851, found 321.0859.

Alternative procedure:

To a solution of aryl amine **203** (400 mg, 2.19 mmol) in THF (7 mL) was added *p*-trifluoromethylbenzaldehyde (300 μL, 2.15 mmol) and left to stir

for 18 h. The reaction mixture was cooled to 0 °C over 10 minutes, TFAA (776 μL, 5.48 mmol) was added and left to stir for 30 min at 0 °C. NEt_3 (1.66 mL, 12.0 mmol) was added dropwise and left to stir for 30 min at 0 °C, then stirred for 1h at rt, the reaction mixture was concentrated *in vacuo* to give the crude imine **199b** as a brown oil. Purification by column chromatography (85:15 Hexanes:Et_2O) gave imine **199b** as a brown/green oily solid (96 mg, 28%). Data same as above.

(*E*)-*N*-(2-((*E*)-2-Nitrovinyl)phenyl)-1-(*p*-tolyl)methanimine **199c**



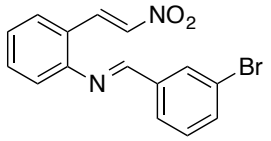
Prepared using general procedure **A.** *p*-Tolualdehyde (240 mg, 2.00 mmol) gave the crude nitrostyrene **199c** as a brown solid. Purification by column chromatography (9:1 Hexanes:EtOAc) gave the pure nitrostyrene **199c** as a yellow oil (500 mg, 94%); R_f = 0.29 (8:2 Hexanes:Et_2O); IR ν_{max} (neat) 1503 (N-O), 1370 (C-H), 1334 (N-O), 965 (C-H) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.42 (1H, d, *J* = 13.6 Hz, C*H*), 8.39 (1H, s, C*H*N), 7.86 (2H, d, *J* = 8.0 Hz, Ar*H*), 7.76 (1H, d, *J* = 13.6 Hz, C*H*), 7.58 (1H, dd, *J* = 7.7, 1.1 Hz, Ar*H*), 7.51 (1H, td, *J* = 7.7, 1.3 Hz, Ar*H*), 7.35 (2H, d, *J* = 7.9 Hz, Ar*H*), 7.30 (1H, td, *J* = 7.6, 1.0 Hz, Ar*H*), 7.08 (1H, d, *J* = 7.9 Hz, Ar*H*), 2.47 (3H, s, ArCH_3); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 161.3 (*C*HN), 152.6 (Ar*C*), 143.0 (Ar*C*), 138.6 (*C*H), 136.5 (*C*H), 133.1 (Ar*C*), 133.0 (Ar*C*H), 130.2 (Ar*C*H), 129.8 (Ar*C*H), 129.2 (Ar*C*H), 126.1 (Ar*C*H), 124.4 (Ar*C*), 119.2 (Ar*C*H), 21.7 (*C*H_3); m/z (EI) 220 (100%, M^+-NO_2); HRMS $C_{16}H_{14}N_2O_2$ calcd. 266.1055, found 266.1050.

Alternative procedure:

To a solution of aryl amine **203** (500 mg, 2.74 mmol) in THF (5 mL) was added *p*-tolualdehyde (330 μL, 2.75 mmol) and left to stir for 18 h. The reaction mixture was cooled to 0 °C over 10 min, TFAA (776 μL, 5.48 mmol) was added and left to stir for 30 min at 0 °C. NEt_3 (1.66 mL, 12 mmol) was added dropwise and left to stir for 30 min at 0 °C, then

brought to rt over 10 min, the reaction mixture was concentrated *in vacuo* to give the crude imine **199c** as a dark brown oil. Purification by column chromatography (8:2 Hexanes:Et_2O) gave imine **199c** as a yellow oil (200 mg, 27%). Data same as above.

(*E*)-1-(3-Bromophenyl)-*N*-(2-((*E*)-2-nitrovinyl)phenyl)methanimine **199d**



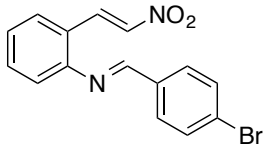
Prepared using general procedure **A**. *m*-bromobenzaldehyde (370 mg, 2.00 mmol) gave the crude nitrostyrene **199d** as a red wax. Purification by column chromatography (9:1 Hexanes:EtOAc) gave the pure nitrostyrene **199d** as a yellow solid (629 mg, 95%); mp 105-107 °C; R_f = 0.30 (8:2 pet. Ether:Et_2O); IR ν_{max} (neat) 3107 (C-H), 1614 (C=N), 1503 (N-O), 1334 (N-O) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.43 (1H, d, *J* = 13.7 Hz, C*H*), 8.37 (1H, s, C*H*N), 8.09 (1H, s, Ar*H*), 7.90 (1H, d, *J* = 7.6 Hz, Ar*H*), 7.68 (1H, d, *J* = 1.1 Hz, Ar*H*), 7.68 (1H, d, *J* = 13.7 Hz, C*H*), 7.60 (1H, d, *J* = 7.7 Hz, Ar*H*), 7.50-7.56 (1H, m, Ar*H*), 7.40-7.43 (1H, m, Ar*H*), 7.39-7.45 (1H, m, Ar*H*), 7.33 (1H, t, *J* = 7.6 Hz, Ar*H*), 7.07 (1H, d, *J* = 7.9 Hz, Ar*H*); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 159.9 (*C*HN), 151.7 (Ar*C*), 138.5 (*C*H), 137.5 (Ar*C*), 136.0 (*C*H), 135.0 (Ar*C*H), 133.0 (Ar*C*H), 132.0 (Ar*C*H), 130.6 (Ar*C*H), 129.7 (Ar*C*H), 127.6 (Ar*C*H), 126.8 (Ar*C*H), 124.5 (Ar*C*), 123.2 (Ar*C*), 119.0 (ArC*H*); m/z (CI) 331 (100%, $M+H^+$), 286 (45%, $M-NO_2^+$); HRMS $C_{15}H_{12}(^{79}Br)N_2O_2$ calcd. 331.0082, found 331.0079.

Alternative procedure:

To aryl amine **203** (328 mg, 1.80 mmol) in THF (4 mL) was added *m*-bromobenzaldehyde (210 μL, 1.80 mmol) and left to stir for 72 h. The reaction mixture was cooled to 0 °C over 30 min, TFAA (510 μL, 3.60 mmol) was added and left to stir for 30 min at 0 °C. NEt_3 (1.25 mL, 9.00 mmol) was added dropwise and left to stir for 30 min at 0 °C, then stirred for 1 h at rt, the reaction mixture was concentrated *in vacuo* to give the crude imine **199d** as a orange/red oil. Purification by column

chromatography (85:15 Hexanes:Et_2O) gave imine **199d** as a bright yellow solid (188 mg, 32%). Data same as above.

(*E*)-1-(4-Bromophenyl)-*N*-(2-((*E*)-2-nitrovinyl)phenyl)methanimine **199e**

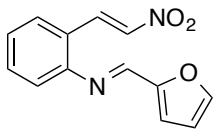


Prepared using general procedure **A**. *p*-Bromobenzaldehyde (370 mg, 2.00 mmol) gave the crude nitrostyrene **199e** as a red gum. Purification by column chromatography (9:1 Hexanes:EtOAc) gave the pure nitrostyrene **199e** as a yellow wax (652 mg, 44%); R_f = 0.30 (9:1 pet. Ether:EtOAc); IR ν_{max} (neat) 1621 (C=N), 1559 (N-O) cm^{-1}; ^1H NMR ($CDCl_3$ 600 MHz) δ 8.43 (1H, d, *J* = 13.9 Hz, C*H*), 8.39 (1H, s, C*H*N), 7.83 (2H, d, *J* = 7.9 Hz, Ar*H*), 7.66 - 7.73 (3H, m, C*H*), 7.59 (1H, d, *J* = 7.9 Hz, Ar*H*), 7.52 (1H, s, Ar*H*), 7.33 (1H, t, *J* = 7.5 Hz, Ar*H*), 7.09 (1H, d, *J* = 7.9 Hz, Ar*H*); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 160.1 (*C*HN), 151.9 (Ar*C*), 138.5 (*C*H), 136.1 (*C*H), 134.3 (Ar*C*), 133.1 (Ar*C*H), 132.4 (Ar*C*H), 130.5 (Ar*C*H), 129.9 (Ar*C*H), 127.0 (Ar*C*), 126.7 (Ar*C*H), 124.5 (Ar*C*), 119.0 (Ar*C*H); m/z (ESI+) 331 (100%, $M+H^+$); HRMS $C_{16}H_{12}(^{79}Br)N_2O_2$ calcd. 331.0082, found 331.0060.

Alternative procedure:

To a solution of aryl amine **203** (520 mg, 2.86 mmol) in THF (7 mL) was added *p*-bromobenzaldehyde (300 μL, 2.15 mmol) and left to stir for 18 h. The reaction mixture was cooled to 0 °C over 30 min, TFAA (776 μL, 5.48 mmol) was added and left to stir for 30 min at 0 °C. NEt_3 (1.66 mL, 12.0 mmol) was added dropwise and left to stir for 30 min at 0 °C, then stirred for 1h at rt, the reaction mixture was concentrated *in vacuo* to give the crude imine **199e** as an orange oil. Purification by column chromatography (8:2 pet. Ether:Et_2O) gave imine **199e** as a yellow solid solid (100 mg, 11%). Data same as above.

(*E*)-1-(Furan-2-yl)-*N*-(2-((*E*)-2-nitrovinyl)phenyl)methanimine **199f**

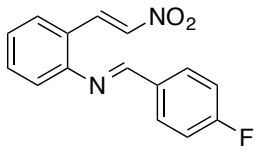


Prepared using general procedure **A**. Furfural (192 mg, 2.00 mmol) gave the crude nitrostyrene **199f** as a red oil. Purification by column chromatography (6:4 Hexanes:Et_2O) gave the pure nitrostyrene **199f** as a brown oil (426 mg, 88%); R_f = 0.14 (8:2 pet. Ether:Et_2O); IR ν_{max} (neat) 1614 (C=N), 1505 (N-O), 1335 (N-O) cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 8.39 (1H, d, *J* = 13.6 Hz, C*H*), 8.24 (1H, s, C*H*N), 7.82 (1H, d, *J* = 13.6 Hz, C*H*), 7.70 (1H, dd, *J* = 1.1, 0.4 Hz, Ar*H*), 7.57 (1H, dd, *J* = 7.7, 1.4 Hz, Ar*H*), 7.50 (1H, td, *J* = 7.7, 1.5 Hz, Ar*H*), 7.30 (1H, td, *J* = 7.5, 1.0 Hz, Ar*H*), 7.10 (1H, dd, *J* = 3.5, 0.4 Hz, Ar*H*), 7.07 (1H, dd, *J* = 7.9, 1.0 Hz, A*rH*), 6.63 (1H, dd, *J* = 3.5, 1.7 Hz, Ar*H*); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 152.0 (*C*H), 151.8 (*C*H), 148.8 (*C*HN), 146.6 (Ar*C*), 138.7 (Ar*C*), 136.4 (*C*H), 132.9 (*C*H), 130.3 (*C*H), 126.4 (*C*H), 124.5 (*C*H), 118.9 (*C*H), 117.4 (Ar*C*), 112.6 (*C*H); m/z (EI) 243 (100%, $M+H^+$), 196 (58%, $M-NO_2^+$); HRMS $C_{13}H_{10}N_2O_3$ calcd. 243.0770, found 243.0763.

Alternative procedure:

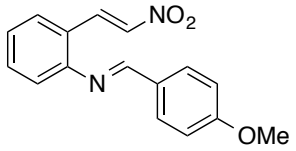
To a solution of aryl amine **203** (400 mg, 2.19 mmol) in THF (7 mL) was added furfural (227 μL, 2.74 mmol) and left to stir for 26 h. The reaction mixture was cooled to 0 °C over 30 min, TFAA (776 μL, 5.48 mmol) was added and left to stir for 30 min at 0 °C. NEt_3 (1.66 mL, 12 mmol) was added dropwise and left to stir for 30 min at 0 °C, then stirred for 1 h at rt, the reaction mixture was concentrated *in vacuo* to give the crude imine **199f** as an orange oil. Purification by column chromatography (6:4 Hexanes:Et_2O) gave imine **199f** as a brown/green oily solid (140 mg, 26%). Data same as above.

(*E*)-1-(4-Fluorophenyl)-*N*-(2-((*E*)-2-nitrovinyl)phenyl)methanimine **199g**



Prepared using general procedure **A**. *p*-Fluorobenzaldehyde (321 µL, 3.00 mmol) gave the crude nitrostyrene **199g** as a red oil. Purification by column chromatography (9:1 Hexanes:EtOAc) gave the pure nitrostyrene **199g** as a yellow wax (760 mg, 94%); R_f = 0.30 (9:1 pet. Ether:EtOAc); IR ν_{max} (neat) 1626 (C=N), 1505 (N-O), 1332 (N-O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.43 (1H, d, *J* = 13.7 Hz, C*H*), 8.39 (1H, s, C*H*N), 7.93-8.00 (2H, m, Ar*H*), 7.71 (1H, d, *J* = 13.7 Hz, C*H*), 7.57-7.60 (1H, m, Ar*H*), 7.48-7.55 (1H, m, Ar*H*), 7.31 (1H, td, *J* = 7.6, 1.2 Hz, Ar*H*), 7.16-7.28 (2H, m, Ar*H*), 7.07 (1H, dd, *J* = 7.9, 1.2 Hz, Ar*H*); ^{13}C NMR ($CDCl_3$ 126 MHz) δ 165.3 (d, *J* = 254.1 Hz, Ar*C*F), 160.1 (*C*HN), 152.2 (Ar*C*), 138.6 (*C*H), 136.4 (*C*H), 133.2 (Ar*C*H), 132.1 (d, *J* = 3.2 Hz, Ar*C*), 131.4 (d, *J* = 8.6 Hz, Ar*C*H), 130.0 (Ar*C*H), 126.5 (Ar*C*H), 124.6 (Ar*C*), 119.1 (ArCH), 116.5 (d, *J* = 22.0 Hz, Ar*C*H); ^{19}F ($CDCl_3$, 282 MHz) 106.30 (C*F*); m/z (CI) 271 (100%, $M+H^+$); HRMS $C_{15}H_{12}FN_2O_2$ calcd. 271.0883, found 271.0893.

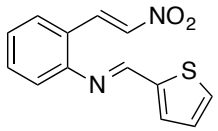
(*E*)-1-(4-Methoxyphenyl)-*N*-(2-((*E*)-2-nitrovinyl)phenyl)methanimine **199h**



Prepared using general procedure **A**. *p*-Anisaldehyde (272 mg, 2.00 mmol) gave the crude nitrostyrene **199h** as a red wax. Purification by column chromatography (9:1 Hexanes:EtOAc) and trituration of the compound (Et_2O) gave the pure nitrostyrene **199h** as a yellow solid (288 mg, 51%); mp 108-110 °C; R_f = 0.36 (8:2 pet. Ether:EtOAc); IR ν_{max} (neat) 1681 (C=N), 1509 (N-O), 1333 (N-O), 1253 (C-O) cm^{-1}; ^1H NMR

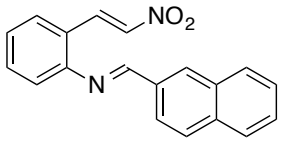
($CDCl_3$, 500 MHz) δ 8.43 (1H, d, *J* = 13.7 Hz, C*H*) 8.35 (1H, s, C*H*N), 7.92 (1H, d, *J* = 8.8 Hz, Ar*H*), 7.77 (1H, d, *J* = 13.7 Hz, C*H*), 7.57 (1H, d, *J* = 8.7 Hz, Ar*H*), 7.51 (1H, t, *J* = 7.0 Hz, Ar*H*), 7.29 (1H, d, *J* = 6.8 Hz, Ar*H*), 7.07 (1H, d, *J* = 7.9 Hz, Ar*H*), 7.05 (2H, d, *J* = 8.8 Hz, Ar*H*), 3.91 (3H, s, OCH_3); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 162.9 (Ar*C*), 160.6 (*C*HN), 152.7 (Ar*C*), 138.5 (*C*H), 136.6 (*C*H), 133.0 (Ar*C*H), 131.0 (Ar*C*H), 130.2 (Ar*C*H), 128.6 (Ar*C*), 125.9 (Ar*C*H), 124.3 (Ar*C*), 119.2 (Ar*C*H), 114.5 (Ar*C*H), 55.5 (CH_3); m/z (CI) 283 (100%, M+H^+), 236 (31%, M-NO_2^+); HRMS $C_{16}H_{15}N_2O_3$ calcd. 283.1084, found 283.1082.

(*E*)-*N*-(2-((*E*)-2-Nitrovinyl)phenyl)-1-(thiophen-2-yl)methanimine **199i**



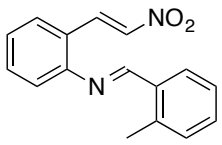
Prepared using general procedure **A**. 2-Thiophenecarboxaldehyde (224 mg, 2.00 mmol) gave the crude nitrostyrene **199i** as a red oil. Purification by column chromatography (85:15 Hexanes:EtOAc) gave the pure nitrostyrene **199i** as a red oil (444 mg, 86%); R_f = 0.30 (9:1 pet. Ether:EtOAc); IR ν_{max} (neat) 2920 (C-H), 1626 (C=N), 1510 (N-O), 1334 (N-O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.52 (1H, s, C*H*N), 8.33 (1H, d, *J* = 13.7 Hz, C*H*), 7.80 (1H, d, *J* = 13.7 Hz, C*H*), 7.59 (1H, d, *J* = 5.0 Hz, Ar*H*), 7.55 (1H, d, *J* = 3.6 Hz, Ar*H*), 7.53 (1H, d, *J* = 7.7 Hz, Ar*H*), 7.45-7.50 (1H, m, Ar*H*), 7.23-7.33 (2H, m, Ar*H*), 7.17 (1H, dd, *J* = 4.9, 3.8 Hz, Ar*H*), 7.08 (1H, d, *J* = 7.9 Hz, Ar*H*); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 153.8 (*C*HN), 151.5 (Ar*C*), 142.3 (Ar*C*), 138.9 (*C*H), 136.3 (*C*H), 133.2 (Ar*C*H), 132.8 (Ar*C*H), 131.9 (Ar*C*H), 130.7 (Ar*C*H), 128.1 (Ar*C*H), 126.4 (Ar*C*H), 124.4 (Ar*C*), 118.9 (Ar*C*H); m/z (CI) 259 (100%, M+H^+), 212 (39%, M-NO_2^+); HRMS $C_{13}H_{11}N_2O_2S$ calcd. 259.0541, found 259.0539.

(*E*)-1-(Naphthalen-2-yl)-*N*-(2-((*E*)-2-nitrovinyl)phenyl)methanimine **199j**



Prepared using general procedure **A**. 2-Napthaldehyde (302 mg, 2.00 mmol) gave the crude nitrostyrene **199j** as a brown solid. Purification by column chromatography (9:1 Hexanes:EtOAc) gave the pure nitrostyrene **199j** as a brown solid (462 mg, 73%); mp 105-107 °C; R_f = 0.40 (6:4 pet. Ether:Et_2O); IR ν_{max} (neat) 1613 (C=N), 1507 (N-O), 1333 (N-O) cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 8.59 (1H, s, C*H*N), 8.50 (1H, d, *J* = 13.6 Hz, C*H*), 8.22-8.26 (2H, m, Ar*H*), 7.96-8.00 (2H, m, Ar*H*), 7.93 (1H, d, *J* = 7.9 Hz, Ar*H*), 7.79 (1H, d, *J* = 13.6 Hz, C*H*), 7.57-7.63 (3H, m, Ar*H*), 7.55 (1H, td, *J* = 7.7, 1.4 Hz, Ar*H*), 7.33 (1H, td, *J* = 7.6, 0.9 Hz, Ar*H*), 7.15 (1H, dd, *J* = 8.0, 1.1 Hz, Ar*H*); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 161.4 (*C*HN), 152.3 (Ar*C*), 138.5 (*C*H), 136.4 (*C*H), 135.4 (Ar*C*), 133.4 (Ar*C*), 133.0 (Ar*C*H), 133.0 (Ar*C*), 132.3 (Ar*C*H), 130.0 (Ar*C*H), 129.1 (Ar*C*H), 128.9 (Ar*C*H), 128.1 (Ar*C*H), 128.0 (Ar*C*H), 126.9 (Ar*C*H), 126.4 (Ar*C*H), 124.5 (Ar*C*), 123.6 (Ar*C*H), 119.1 (Ar*C*H); m/z (CI) 303 (100%, $M+H^+$), 256 (34%, $M-NO_2^+$); HRMS $C_{19}H_{15}N_2O_2$ calcd. 303.1134, found 303.1133.

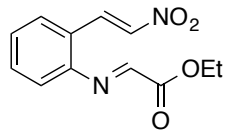
(*E*)-*N*-(2-((*E*)-2-Nitrovinyl)phenyl)-1-(*o*-tolyl)methanimine **199k**



Prepared using general procedure **A**. *o*-Tolualdehyde (240 mg, 2.00 mmol) gave the crude nitrostyrene **199k** as a red oil. Purification by column chromatography (9:1 Hexanes:EtOAc) gave pure nitrostyrene **199k** as a yellow oil (271 mg, 51 %); R_f = 0.25 (9:1 pet. Ether:EtOAc); IR υ_{max} (neat) 1619 (C=N), 1508 (N-O), 1334 (N-O), 1294 (C-H) cm^{-1}; ^1H

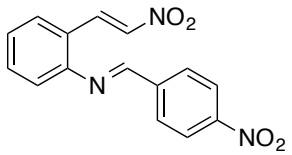
NMR ($CDCl_3$, 600 MHz) δ 8.72 (1H, s, C*H*N), 8.46 (1H, d, *J* = 13.7 Hz, C*H*), 8.14 (1H, dd, *J* = 7.8, 1.3 Hz, Ar*H*), 7.74 (1H, d, *J* = 13.6 Hz, C*H*NO_2), 7.59 (1H, dd, *J* = 7.8, 1.4 Hz, Ar*H*), 7.54 (1H, td, *J* = 7.7, 1.4 Hz, Ar*H*), 7.43 (1H, td, *J* = 7.5, 1.5 Hz, Ar*H*), 7.38 (1H, t, *J* = 7.7 Hz, Ar*H*), 7.32 (1H, td, *J* = 7.6, 1.1 Hz, Ar*H*), 7.29 (1H, d, *J* = 7.6 Hz, Ar*H*), 7.07 (1H, dd, *J* = 7.9, 1.0 Hz Ar*H*), 2.66 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 121 MHz) 160.2 (*C*HN), 152.8 (Ar*C*), 139.2 (Ar*C*), 138.2 (*C*H), 136.3 (*C*H), 133.3 (Ar*C*), 133.0 (Ar*C*H), 131.8 (Ar*C*H), 131.4 (Ar*C*H),129.7 (Ar*C*H), 128.6 (Ar*C*H),126.6 (Ar*C*H), 126.2 (Ar*C*H), 124.2 (Ar*C*), 119.2 (Ar*C*H), 19.6 (*C*H_3); m/z (CI) 267 (100%, M+H^+), 220 (23%, M-NO_2^+); HRMS $C_{16}H_{15}N_2O_2$ calcd. 267.1134, found 267.1133.

Ethyl-(*E*)-2-((2-((*E*)-2-nitrovinyl)phenyl)imino)acetate **199l**



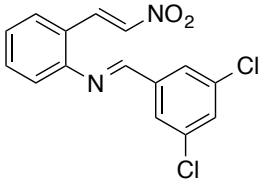
Prepared using general procedure **A**. Solution of ethylglyxoylate (50% w/w in toluene, 792 µL, 4.00 mmol) gave the crude nitrostyrene **199l** as a red gum. Purification by column chromatography (7:3 Hexanes:EtOAc) gave the pure nitrostyrene **199l** as a red oil (150 mg, 15%); R_f = 0.32 (7:3 pet. Ether:EtOAc); IR ν_{max} (neat) 1713 (C=O), 1625 (C=N), 1503 (N-O) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.26 (1H, d, *J* = 13.8 Hz, C*H*), 7.85 (1H, s, C*H*N), 7.78 (1H, d, *J* = 13.6 Hz, C*H*), 7.59 (1H, d, *J* = 7.7 Hz, Ar*H*), 7.51 (1H, t, *J* = 7.7 Hz, Ar*H*), 7.39 (1H, t, *J* = 7.6 Hz, 1H, Ar*H*), 7.05 (1H, d, *J* = 7.9 Hz, Ar*H*), 4.43 (2H, q, *J* = 7.1 Hz, CH_2), 1.43 (3H, t, *J* = 7.1 Hz, CH_2CH_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.7 (*C*O), 152.6 (*C*HN), 149.0 (Ar*C*), 139.6 (*C*H), 135.3 (*C*H), 132.9 (Ar*C*H), 130.6 (Ar*C*H), 128.8 (Ar*C*H), 125.2 (Ar*C*), 118.5 (Ar*C*H), 62.5 (*C*H_2), 14.2 (*C*H_3); m/z (ESI+) 247 (100%, M-H^+); HRMS $C_{12}H_{12}N_2O_4$ calcd. 247.0719, found 247.0725.

(*E*)-1-(4-Nitrophenyl)-*N*-(2-((*E*)-2-nitrovinyl)phenyl)methanimine **199m**



Prepared using general procedure **A**. *p*-Nitrobenzaldehyde (302 mg, 2.00 mmol) gave the crude nitrostyrene **199m** as a red wax. Purification by column chromatography (7:3 Hexanes:EtOAc) gave the pure nitrostyrene **199m** as a yellow solid (487 mg, 82%); mp 131-133 °C; R_f = 0.38 (7:3 Hexanes:EtOAc); IR ν_{max} (neat) 1630 (C=N), 1523 (N-O), 1333 (N-O) cm^{-1} ^1H NMR ($CDCl_3$, 600 MHz) δ 8.56 (1H, s, C*H*N), 8.49 (1H, d, *J* = 13.6 Hz, C*H*), 8.40 (2H, d, *J* = 8.7 Hz, Ar*H*), 8.15 (2H, d, *J* = 8.7 Hz, Ar*H*), 7.68 (1H, d, *J* = 13.9 Hz, C*H*), 7.64 (1H, d, *J* = 7.5 Hz, Ar*H*), 7.57 (1H, t, *J* = 7.7 Hz, Ar*H*), 7.39 (1H, t, *J* = 7.5 Hz, Ar*H*), 7.15 (1 H, d, *J* = 7.9 Hz, Ar*H*); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 158.9 (*C*HN), 151.0 (Ar*C*), 149.7 (Ar*C*), 140.7 (Ar*C*), 138.5 (*C*H), 135.7 (*C*H), 133.1 (Ar*C*H), 129.8 (Ar*C*H), 129.5 (Ar*C*H), 127.5 (Ar*C*H), 124.9 (Ar*C*), 124.3 (Ar*C*H), 118.8 (Ar*C*H); m/z (EI) 251 (100%, M-NO_2^+), 204 (72%, M-$N_2O_2H^+$); HRMS $C_{15}H_{11}N_3O_4$ calcd. 297.0750, found 297.0751; Anal. calcd. for $C_{15}H_{11}N_3O_4$: C, 60.61; H, 6.73; N, 14.14; found: C, 60.49; H, 3.63; N, 14.11%.

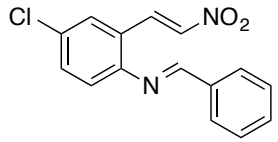
(*E*)-1-(3,5-Dichlorophenyl)-*N*-(2-((*E*)-2-nitrovinyl)phenyl)methanimine **199n**



Prepared using general procedure **A**. 3,5-dichlorobenzaldehyde (696 mg, 4.00 mmol) gave the crude nitrostyrene **199n** as an orange solid. The crude nitrostyrene **199n** was added Et_2O and then solids filtered to give the pure nitrostyrene **199n** as a yellow solid (538 mg, 42%); R_f = 0.31 (9:1 pet. Ether:EtOAc); mp 163-165 °C (dec.); IR υ_{max} (neat) 1623 (C=N), 1505 (N-O), 1334 (N-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.43 (1H, d, *J*

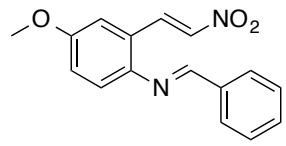
= 13.8 Hz, C*H*), 8.33 (1H, s, C*H*N), 7.84 – 7.80 (2H, m, Ar*H*), 7.64 (1H, d, *J* = 13.7 Hz, C*H*), 7.61 (1H, dd, *J* = 7.8, 1.4 Hz, Ar*H*), 7.56 – 7.50 (2H, m, Ar*H*), 7.35 (1H, td, *J* = 7.6, 1.2 Hz, Ar*H*), 7.05 (1H, dd, *J* = 8.0, 1.1 Hz, ArH); ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.8 (*C*HN), 151.3 (Ar*C*), 138.5 (*C*H), 138.4 (Ar*C*), 136.0 (Ar*C*H), 135.9 (*C*H), 133.2 (Ar*C*H), 132.0 (Ar*C*H), 129.5 (Ar*C*H), 127.4 (Ar*C*H), 127.3 (Ar*C*H), 124.7 (Ar*C*), 119.1 (Ar*C*H); m/z (ESI+) 343 (100%, M+Na$^+$); HRMS $C_{15}H_{10}Cl_2N_2O_2Na$ calcd. 343.0017, found 343.0019.

(*E*)-*N*-(4-Chloro-2-((*E*)-2-nitrovinyl)phenyl)-1-phenylmethanimine **199r**



Prepared using general procedure **A**. Styrene **229b** (306 mg, 2.00 mmol) gave **199r** as a yellow solid (534 mg, 93%); mp 128-130 °C; R_f = 0.28 (9:1 pet.Ether:EtOAc); IR ν_{max} (neat) 3110 (C-H), 1615 (C=N), 1576 (C=C), 1508 (N-O), 1332 (N-O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.43 (1H, s, C*H*N), 8.37 (1H, d, *J* = 13.6 Hz, C*H*), 7.96 (1H, dd, *J* = 8.2, 1.3 Hz, Ar*H*), 7.72 (1H, d, *J* = 13.7 Hz, C*H*), 7.53 - 7.60 (5H, m, Ar*H*), 7.48 (1H, dd, *J* = 8.5, 2.3 Hz, Ar*H*), 7.06 (1H, d, *J* = 8.5 Hz, Ar*H*); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 162.0 (*C*HN), 150.6, (Ar*C*) 135.4 (*C*H), 139.3 (*C*H), 135.1 (Ar*C*), 132.8 (Ar*C*H), 132.6, (Ar*C*H) 132.0, (Ar*C*) 129.4 (2x Ar*C*H), 129.2 (Ar*C*H), 126.0 (Ar*C*), 120.5 (Ar*C*H); m/z (ESI+) 287 (100%, M+H$^+$); HRMS $C_{15}H_{12}ClN_2O_2$ calcd. 287.0587, found 287.0597

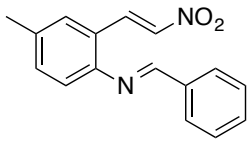
(*E*)-*N*-(4-Methoxy-2-((*E*)-2-nitrovinyl)phenyl)-1-phenylmethanimine **199s**



Prepared using general procedure **A**. Styrene **229c** (149 mg, 1.00 mmol) gave the crude nitrostyrene **199s** as a red oil. Purification by column chromatography (9:1 Hexanes:EtOAc) gave pure nitrostyrene **199s** as a red solid (80 mg, 28%); mp 85-87 °C; R_f = 0.18 (8:2 pet. Ether:Et_2O); IR

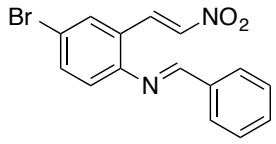
υ_{max} (neat) 1622 (C=N), 1496 (N-O), 1338 (N-O), 1290 (C-O) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.50 (1H, d, *J* = 13.7 Hz, C*H*), 8.44 (1H, s, C*H*N), 7.94 (2H, dd, *J* = 7.2, 2.1 Hz, Ar*H*), 7.74 (1H, d, *J* = 13.6 Hz, C*H*NO_2), 7.47 - 7.60 (3H, m, Ar*H*), 7.03 - 7.16 (3H, m, Ar*H*), 3.87 (3H, s, OCH_3); ^{13}C NMR ($CDCl_3$, 151 MHz) 160.0 (*C*HN), 158.2 (Ar*C*), 145.6 (Ar*C*), 138.7 (*C*H), 136.5 (*C*H), 135.9 (Ar*C*), 132.0 (Ar*C*H), 129.1 (Ar*C*H), 129.1 (Ar*C*H), 125.9 (Ar*C*), 120.0 (Ar*C*H), 119.3 (Ar*C*H), 113.7 (Ar*C*H), 55.8 (OCH_3); m/z (EI) 282 (27%, M+), 236 (100%, M-NO_2^+); HRMS $C_{16}H_{14}N_2O_3$ calcd. 282.1004, found 282.1010.

(*E*)-*N*-(4-Methyl-2-((*E*)-2-nitrovinyl)phenyl)-1-phenylmethanimine **199t**



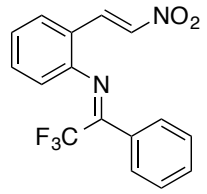
Prepared using general procedure **A**. Styrene **229d** (266 mg, 2.00 mmol) gave crude nitrostyrene **199t** as a red oil. Purification by column chromatography (9:1 pet. Ether:EtOAc) gave pure nitrostyrene **199t** as an orange solid (335 mg, 63%); mp 110-112 °C; R_f = 0.33 (9:1 pet. Ether:EtOAc); IR υ_{max} (neat) 3106 (C-H), 1615 (C=C), 1503 (N-O), 1330 (N-O) cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 8.44 (1H, s, C*H*N), 8.44 (1H, d, *J* = 13.6 Hz, C*H*), 7.96 (2H, dd, *J* = 7.7, 1.7 Hz, Ar*H*), 7.76 (1H, d, *J* = 13.9 Hz, C*H*NO_2), 7.51 - 7.58 (3H, m, Ar*H*), 7.40 (1H, s, Ar*H*), 7.33 (1H, dd, *J* = 8.1, 1.3 Hz, Ar*H*), 7.03 (1H, d, *J* = 7.9 Hz, Ar*H*), 2.42 (3H, s, ArCH_3); ^{13}C NMR ($CDCl_3$, 151 MHz) 160.8 (*C*HN), 149.8 (Ar*C*), 138.3 (*C*H), 136.5 (*C*H), 136.3 (Ar*C*), 135.7 (Ar*C*), 133.8 (Ar*C*H), 132.0 (Ar*C*H), 130.3 (Ar*C*H), 129.1 (Ar*C*H), 129.0 (Ar*C*H), 124.3 (Ar*C*), 118.8 (Ar*C*H), 20.8 (ArCH_3); m/z (EI) 221 (100%, M-NO_2^+), 266 (33%, M^+); HRMS $C_{16}H_{14}N_2O_2$ calcd. 266.1055, found 266.1052. Anal. calcd. for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found C, 71.81; H, 5.32; N, 10.41%.

(*E*)-*N*-(4-Bromo-2-((*E*)-2-nitrovinyl)phenyl)-1-phenylmethanimine **199u**



Prepared using general procedure **A**. **229e** (891 mg, 4.50 mmol) gave the crude nitrostyrene **199u** as a brown solid. Purification by column chromatography (9:1 Hexanes:EtOAc) gave the pure nitrostyrene **199u** as a tan solid (645 mg, 43%); mp 156-158 °C; R_f = 0.35 (9:1 pet. Ether:EtOAc); IR ν_{max} (neat) 1618 (C=N), 1332 (N-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.41 (s, 1H, C*H*N), 8.34 (1H, d, *J* = 13.7 Hz, C*H*), 7.96 - 7.93 (2H, m, C*H*), 7.72 -7.68 (2H, m, Ar*H*), 7.63 – 7.49 (5H, m, C*H*), 6.98 (1H, d, *J* = 8.4 Hz, Ar*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.0 (*C*HN), 151.1 (Ar*C*), 139.4 (Ar*C*H), 135.7 (Ar*C*H), 135.5 (Ar*C*H), 134.9 (Ar*C*H), 132.7 (Ar*C*H), 132.4 (Ar*C*H), 129.9 (Ar*C*H), 129.5 (Ar*C*H), 129.3 (Ar*C*H), 129.1 (*C*H), 126.5 (Ar*C*), 120.8 (*C*H), 119.7 (Ar*C*), 109.7 (Ar*C*); m/z (CI) 331 (100%, M^+); HRMS $C_{15}H_{12}N_2O_2(^{79}Br)$ calcd. 331.0077, found 331.0076.

(*Z*)-2,2,2-Trifluoro-*N*-(2-((*E*)-2-nitrovinyl)phenyl)-1-phenylethan-1-imine **240a**



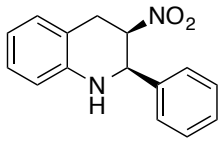
To a solution of aryl azide **242** (290 mg, 2.00 mml) in THF (10.0 mL) was added PPh_3 (524 mg, 2.00 mmol) and left to stir for 30 min. The reaction mixture was added 2,2,2-trifluoroacetophenone (248 µL, 2.00 mmol) and heated to 45 °C for 18 h. The reaction mixture was concentrated *in vacuo* to give the crude imine as a red oil. The crude imine was dissolved in DCE (10 mL) and added $AgNO_2$ (924 mg, 6.00 mmol), 4Å MS (300 mg) and TEMPO (125 mg, 0.80 mmol), the suspension was then heated to 70 °C for 3 h. The reaction mixture was filtered through a pad of Celite (DCM & EtOAc wash) and concentrated *in vacuo* to give the crude nitrostyrene **240a** as a red oil. Purification by column chromatography (9:1 Hexanes:EtOAc) gave the pure nitrostyrene **240a** as an orange solid (291 mg, 45%); mp 102-104 °C ; R_f = 0.15 (9:1 pet.Ether:EtOAc); mp 82-84 °C; IR ν_{max} (neat) 1632 (C=N), 1513 (N-O), 1343 (N-O), 1204 (CF_3) cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 7.99 (1H, d, *J* = 13.7 Hz, C*H*), 7.22 (1H, d, *J* = 13.7 Hz, C*H*), 6.85 (2H, d, *J* = 7.7 Hz, Ar*H*), 6.78 – 6.74 (1H, m, Ar*H*), 6.70 (2H, dd, *J* = 8.4, 6.9 Hz, Ar*H*), 6.61 – 6.55 (2H, m, Ar*H*), 6.51 – 6.46 (1H, m, Ar*H*), 6.12 – 6.07 (1H, m, ArH); ^{13}C NMR (151 MHz, DMSO) δ 158.6 (Ar*C*), 158.4 (*C*H), 153.3 (*C*H), 146.9 (Ar*C*H), 138.8 (Ar*C*H), 134.2 (Ar*C*H), 132.7 (Ar*C*H), 131.1 (Ar*C*H), 129.5 (Ar*C*H), 128.9 (Ar*C*H), 128.3 (Ar*C*H), 126.3 (Ar*C*H), 121.6 (Ar*C*), 120.0 (Ar*C*H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -69.31 (C*F*$_3$); m/z (ESI+) 321 (100%, M^+H^+); HRMS $C_{16}H_{12}N_2O_2F_3$ calcd. 321.0851, found 321.0844.

5.8 Preparation of 3-nitro-2-aryl-tetrahydroquinolines

General procedure B

A solution of nitrostyrene **199** (0.10 mmol) and catalyst **71** (5.00 μmol) in PhMe (1.00 mL) was added Hantzsch ester **68** (0.10 mmol) and left to stir for 18 h at 0 °C. The reaction mixture was concentrated *in vacuo* to give the crude tetrahydroquinoline **175**, which was purified by column chromatography (1:1 Hexanes:DCM).

(2*R*,3*R*)-3-Nitro-2-phenyl-1,2,3,4-tetrahydroquinoline **175a**

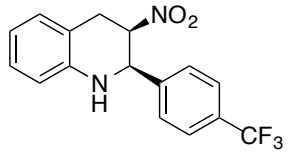


Prepared using general procedure **B**. Nitrostyrene **199a** (25.0 mg, 0.10 mmol) gave **175a** as a yellow solid (32 mg, 93%); mp 136-137 °C; Enantiomeric excess 97%; R_f = 0.28 (9:1 Hexanes:EtOAc); $[\alpha]_D^{20}$= 85.9 (c = 0.17, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) 7.30-7.35 (3H, m, Ar*H*), 7.20-7.23 (2H, m, Ar*H*), 7.13 (1H, t, *J* = 7.5 Hz, Ar*H*), 7.09 (1H, d, *J* = 7.5 Hz, Ar*H*), 6.78 (1H, td, *J* = 7.4, 0.9 Hz, Ar*H*), 6.67 (1H, d, *J* = 7.9 Hz, Ar*H*), 5.14 (1H, ddd, *J* = 8.7, 4.7, 4.7 Hz, C*H*NO_2), 5.09 (1H, d, *J* = 4.1 Hz, C*H*Ph), 4.25-4.59 (1H, br. s, N*H*), 3.30 (1H, dd, *J* = 16.7, 8.7 Hz, C*H*H), 3.26 (1H, dd, *J* = 16.7, 5.3 Hz, CH*H*); HPLC analysis: Daicel Chiralpak OD, hexane/*iso*-propanol = 1:1, flow rate = 1.0 mL/min, λ = 254 nm, retention time 12.9 min (major) and 19.9 (minor).
Data consistent with literature.[71]

Alternative Procedure (racemic):
A solution of nitrostyrene **199a** (160 mg, 0.63 mmol) in THF (2 mL) was cooled to -78 °C over 30 min. A solution of $LiBHEt_3$ (760 μL, 0.76 mmol, 1.0 M in THF) was added dropwise and the mixture stirred for 30 min, then stirred for 30 min at rt. The reaction mixture was diluted with brine (30 mL), the product was extracted with DCM (3 x 10 mL), the combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated in vacuo to give the crude tetrahydroquinoline **175a** as a red oil. Purification by column chromatography (9:1 Hexanes:Et_2O) gave the

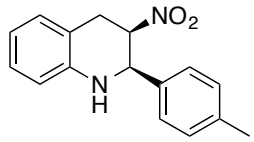
pure tetrahydroquinoline **175a** as a yellow solid (110 mg, 68%); data same as above.

(2*R*,3*R*)-3-Nitro-2-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroquinoline **175b**



Prepared using general procedure **B**. Nitrostyrene **199b** (32.0 mg, 0.10 mmol) gave **175b** as a yellow solid (31 mg, 95%); mp 140-142 °C; Enantiomeric excess >99%; R_f = 0.30 (9:1 pet. Ether:EtOAc); $[\alpha]_D^{20}$= 78.0 (c = 0.38, $CHCl_3$); NMR ($CDCl_3$, 600 MHz) δ 7.57 (2H, d, *J* = 8.0 Hz, Ar*H*), 7.33 (2H, d, *J* = 8.1 Hz, Ar*H*), 7.07-7.18 (2H, m, Ar*H*), 6.80 (1H, t, *J* = 7.5 Hz, Ar*H*), 6.68 (1H, d, *J* = 8.1 Hz, Ar*H*), 5.09-5.29 (2H, m, C*H*NO_2 & C*H*Ar), 4.42 (1H, br. s, N*H*), 3.26 (2H, d, *J* = 7.0 Hz, CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ -62.76 (3F, s, CF_3); HPLC analysis: Daicel Chiralpak OD, hexane/*iso*-propanol = 1:1, flow rate = 1.0 mL/min, λ = 254 nm, retention time 17.1 min (major) and 26.4 (minor).
Data consistent with literature.[71]

(2*R*,3*R*)-3-Nitro-2-(*p*-tolyl)-1,2,3,4-tetrahydroquinoline **175c**

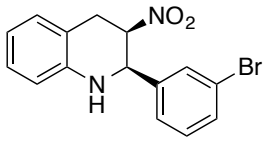


Prepared using general procedure **B**. Nitrostyrene **199c** (25.0 mg, 0.10 mmol) gave **175c** as a yellow solid (27 mg, 100%); mp 142-144 °C; Enantiomeric excess 98%; R_f = 0.30 (9:1 pet. Ether:EtOAc); $[\alpha]_D^{20}$= 93.6 (c = 0.33, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.16 – 7.03 (6H, m, Ar*H*), 6.79 – 6.60 (2H, m, Ar*H*), 5.09 (1H, ddd, *J* = 10.0, 5.4, 4.2 Hz, C*H*NO_2), 5.04 (1H, s, C*H*Ar), 4.36 (1H, br. s, N*H*), 3.38 (1H, dd, *J* = 16.7, 8.4 Hz, C*H*H), 3.27 (1H, dd, *J* = 16.8, 5.3 Hz, CH*H*), 2.33 (3H, s, CH_3); HPLC analysis (Daicel Chiralpak OD, Hexane/*iso*-propanol 50:50, flow rate 1

mL/min, λ = 254 nm): retention time t_r, (major) = 18.0 min, t_r (minor) = 30.6 min.

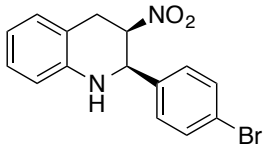
Data consistent with literature.[71]

(2*R*,3*R*)-2-(3-Bromophenyl)-3-nitro-1,2,3,4-tetrahydroquinoline **175d**



Prepared using general procedure **B**. Nitrostyrene **199d** (33.0 mg, 0.10 mmol) gave **175d** as a yellow solid (31 mg, 100%); mp 112-113 °C; Enantiomeric excess 96%; R_f = 0.30 (8:2 pet. Ether:EtOAc); $[\alpha]_D^{20}$= 75.1 (c = 0.20, $CHCl_3$); IR ν_{max} (neat) 3389 (N-H), 1540 (N-O), 1475 (C-H), 1368 (N-O) cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.47 (1H, d, *J* = 7.5 Hz, Ar*H*), 7.38 (1H, s, Ar*H*), 7.18 - 7.22 (1H, m, Ar*H*), 7.12-7.18 (2H, m, Ar*H*), 7.10 (1H, d, *J* = 7.5 Hz, Ar*H*), 6.81 (1H, t, *J* = 7.5 Hz, Ar*H*), 6.67 (1H, d, *J* = 7.9 Hz, Ar*H*), 5.11 (1H, ddd, *J* = 8.3, 5.3, 4.1 Hz, C*H*NO_2), 5.03 (1H, d, *J* = 3.8 Hz, C*H*Ar), 4.25 (1H, br. s, N*H*), 3.30 (1H, dd, *J* = 16.6, 7.9 Hz, C*H*H), 3.25 (1H, dd, *J* = 16.9, 5.6 Hz, CH*H*); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 142.2 (Ar*C*), 140.6 (Ar*C*), 132.0 (Ar*C*H), 130.3 (Ar*C*H), 129.9 (Ar*C*H), 129.6 (Ar*C*H), 128.0 (Ar*C*H), 125.4 (Ar*C*H), 122.8 (Ar*C*), 118.8 (Ar*C*H), 115.9 (Ar*C*), 114.1 (Ar*C*H), 82.3 (*C*HNO_2), 56.6 (*C*HAr), 27.6 (*C*H_2); m/z (CI) 286 (100%, M-NO_2); HRMS (CI) calcd. for $C_{15}H_{14}(^{79}Br)N_2O_2$: 333.0239, found 333.0225; HPLC analysis: Daicel Chiralpak OD, hexane/*iso*-propranol = 1:1, flow rate = 1.0 mL/min, λ = 254 nm, retention time 15.7 min (major) and 28.6 (minor).

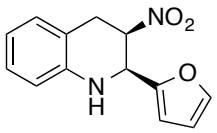
(2*R*,3*R*)-2-(4-Bromophenyl)-3-nitro-1,2,3,4-tetrahydroquinoline **175e**



Prepared using general procedure **B**. Nitrostyrene **199e** (33.0 mg, 0.10 mmol) gave **175e** as a yellow solid (33 mg, 99%); mp 151-153 °C; Enantiomeric excess 98%; R_f = 0.38 (9:1 pet. Ether:EtOAc); $[\alpha]_D^{20}$= 74.7 (c = 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.40 - 7.45 (2H, m, Ar*H*), 7.12 (1H, t, *J* = 7.7 Hz, Ar*H*), 7.06 - 7.09 (3H, m, Ar*H*), 6.78 (1H, t, *J* = 7.4 Hz, Ar*H*), 6.66 (1H, d, *J* = 8.0 Hz, Ar*H*), 5.11 (1H, app. dt, *J* = 8.5, 4.8 Hz, C*H*), 5.07 (1H, br. s, C*H*), 4.37 (1H, br. s, N*H*), 3.18-3.29 (2H, m, CH_2); HPLC analysis: Daicel Chiralpak OD, hexane/*iso*-propanol = 1:1, flow rate = 1.0 mL/min, λ = 254 nm, retention time 19.9 min (major) and 34.3 (minor).

Data consistent with literature.[71]

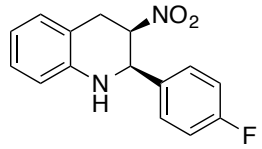
(2*S*,3*R*)-2-(Furan-2-yl)-3-nitro-1,2,3,4-tetrahydroquinoline **175f**



Prepared using general procedure **B**. Nitrostyrene **199f** (24.0 mg, 0.10 mmol) gave **175f** as a brown oil (17 mg, 88%); Enantiomeric excess 88%; R_f = 0.20 (8:2 Hexanes:EtOAc) $[\alpha]_D^{20}$= 89.4 (c = 0.62, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35 (1 H, s, C*H*), 7.05-7.13 (2H, m, C*H*), 6.79 (1H, t, *J* = 7.5 Hz, C*H*), 6.66 (1H, d, *J* = 8.0 Hz, C*H*), 6.31 (1H, m, *J* = 3.1, 1.7 Hz, C*H*), 6.20-6.23 (1H, m, C*H*), 5.23 (1H, d, *J* = 3.6 Hz, C*H*Ar), 5.11 (1H, ddd, *J* = 9.3, 5.2, 3.9 Hz, C*H*NO_2), 4.35 (1H, br. s, N*H*), 3.38 (1H, dd, *J* = 16.6, 9.5 Hz, CH*H*), 3.28 (1H, dd, *J* = 16.6, 5.5 Hz, C*H*H); HPLC analysis: Daicel Chiralpak OD, hexane/*iso*-propanol = 1:1, flow rate = 1.0 mL/min, λ = 254 nm, retention time 9.20 min (major) and 13.2 (minor).

Data consistent with literature.[71]

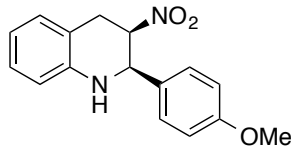
(2*R*,3*R*)-2-(4-Fluorophenyl)-3-nitro-1,2,3,4-tetrahydroquinoline **175g**



Prepared using general procedure **B**. Nitrostyrene **199g** (27.0 mg, 0.10 mmol) gave **175g** as a yellow solid (27 mg, 100%); mp 148-150 °C; Enantiomeric excess >99%; R_f = 0.30 (9:1 pet. Ether:EtOAc); $[\alpha]_D^{20}$= 84.1 (c = 0.15, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.18 (2H, dd, *J* = 7.7, 4.7 Hz, Ar*H*), 7.13 (1H, t, *J* = 7.7 Hz, Ar*H*), 7.09 (1H, d, *J* = 7.6 Hz, Ar*H*), 7.00 (2H, td, *J* = 8.6, 1.6 Hz, Ar*H*), 6.79 (1H, t, *J* = 7.5 Hz, Ar*H*), 6.65 (1H, d, *J* = 8.0 Hz, Ar*H*), 5.05-5.13 (2H, m, *CH*NO_2 *&* C*H*Ar), 4.38 (1H, br. s, N*H*), 3.15-3.32 (2H, m, CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ -112.87 (1F, s, Ar*F*); HPLC analysis: Daicel Chiralpak OD, hexane/*iso*-propranol = 1:1, flow rate = 1.0 mL/min, λ = 254 nm, retention time 16.4 min (major) and 28.0 (minor).

Data consistent with literature.[71]

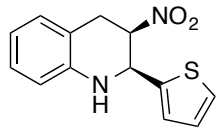
(2*R*,3*R*)-2-(4-Methoxyphenyl)-3-nitro-1,2,3,4-tetrahydroquinoline **175h**



Prepared using general procedure **B**. Nitrostyrene **199h** (28.0 mg, 0.10 mmol) gave **175h** as a yellow solid (28 mg, 97%); mp 144-146 °C; Enantiomeric excess >99%; R_f = 0.30 (9:1 pet. Ether:EtOAc); $[\alpha]_D^{20}$= 67.9 (c = 0.34 , $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.06 - 7.15 (4H, m, Ar*H*), 6.87 – 6.81 (2H, m, Ar*H*), 6.74-6.79 (1H, m, Ar*H*), 6.64 (1H, d, *J* = 8.0 Hz, Ar*H*), 5.09 (1H, ddd, *J* = 8.9, 4.4 Hz, C*H*NO_2), 5.03 (1H, d, *J* = 4.1 Hz, C*H*Ar), 4.35 (1H, br. s, N*H*), 3.78 (3H, s, OCH_3), 3.29 (1H, dd, *J* = 16.7, 8.5 Hz, CH*H*), 3.22 (1H, dd, *J* = 16.6, 5.3 Hz, C*H*H); HPLC analysis: Daicel Chiralpak OD, hexane/*iso*-propranol = 1:1, flow rate = 1.0 mL/min, λ = 254 nm, retention time 17.9 min (major) and 31.0 (minor).

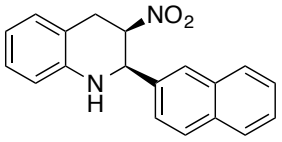
Data consistent with literature.[71]

(2*S*,3*R*)-3-Nitro-2-(thiophen-2-yl)-1,2,3,4-tetrahydroquinoline **175i**



Prepared using general procedure **B**. Nitrostyrene **199i** (40.0 mg, 0.16 mmol) gave **175i** as a red oil (39 mg, 97%); Enantiomeric excess 99%; R_f = 0.30 (9:1 pet. Ether:EtOAc); $[\alpha]_D^{20}$= 46.0 (c = 0.15, $CHCl_3$); IR ν_{max} (neat) 3398 (N-H), 1545 (N-O), 1369 (N-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.11-7.14 (1H, m, C*H*), 7.08-7.10 (1H, m, C*H*), 6.94 (1H, dd, *J* = 5.1, 3.6 Hz, C*H*), 6.88-6.91 (1H, m, C*H*), 6.80 (1H, td, *J* = 7.5, 1.1 Hz, C*H*), 6.65 (1H, dd, *J* = 8.0, 1.1 Hz, C*H*), 5.47 (1H, d, *J* = 4.2 Hz, C*H*), 5.09 (1H, ddd, *J* = 10.0, 5.4, 4.2 Hz, C*H*NO_2), 4.52 (1H, br. s, N*H*), 3.38 (1H, dd, *J* = 16.5, 10.3 Hz, C*H*H), 3.27 (1H, dd, *J* = 16.5, 5.5 Hz, CH*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 141.7 (Ar*C*), 140.8 (Ar*C*), 129.8 (Ar*C*H), 128.2 (Ar*C*H), 127.2 (Ar*C*H), 126.1 (Ar*C*H), 125.9 (Ar*C*), 119.1 (Ar*C*H), 116.3 (Ar*C*H), 114.7 (Ar*C*H), 82.2 (*C*HNO_2), 53.3 (*C*H), 27.1 (*C*H_2); m/z (ESI+) 211 (100%, $M+H^+$); HRMS (ESI+) calcd. for $C_{13}H_{13}N_2O_2S$: 261.0698, found 261.0703; HPLC analysis: Daicel Chiralpak OD, hexane/*iso*-propanol = 1:1, flow rate = 1.0 mL/min, λ = 254 nm, retention time 18.0 min (major) and 30.6 (minor).

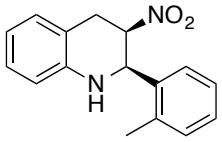
(2*R*,3*R*)-2-(Naphthalen-2-yl)-3-nitro-1,2,3,4-tetrahydroquinoline **175j**



Prepared using general procedure **B**. Nitrostyrene **199j** (30.0 mg, 0.10 mmol) gave **175j** as a brown oil (31 mg, 100%); Enantiomeric excess 98%; R_f = 0.38 (8:2 pet. Ether:EtOAc) $[\alpha]_D^{20}$= 63.6 (c = 0.38, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) δ 7.76 - 7.86 (3H, m, ArC*H*), 7.71 (1H, s, ArC*H*), 7.46-7.52 (2H, m, ArC*H*), 7.32 (1H, dd, *J* = 8.5, 1.6 Hz, ArC*H*), 7.17 (1H, t, *J* = 7.6 Hz, ArC*H*), 7.12 (1H, d, *J* = 7.4 Hz, ArC*H*), 6.82 (1H, t, *J* = 7.4 Hz, ArC*H*), 6.72 (1H, d, *J* = 7.9 Hz, ArC*H*), 5.24 (1H, d, *J* = 3.6 Hz, C*H*Ar), 5.20-5.24 (1H, m, C*H*NO_2), 4.49 (1H, br. s, N*H*), 3.36 (1H, dd, *J* =

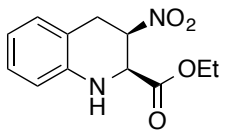
16.9, 8.0 Hz, CH*H*), 3.28 (1H, dd, *J* = 16.8, 5.0 Hz, C*H*H); HPLC analysis: Daicel Chiralpak OD, hexane/*iso*-propanol = 1:1, flow rate = 1.0 mL/min, λ = 254 nm, retention time 23.1 min (major) and 43.1 (minor).
Data consistent with literature.[71]

(2*R**,3*R**)-3-Nitro-2-(*o*-tolyl)-1,2,3,4-tetrahydroquinoline **175k**



Prepared using general procedure **B**. Nitrostyrene **199k** (25.0 mg, 0.10 mmol) gave **175k** as a yellow wax (27.0 mg, 100% yield); R_f = 0.19 (9:1 pet. Ether:EtOAc); IR ν_{max} (neat) 3387 (N-H), 1547 (N-O), 1335 (N-O) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.35 (1H, m, Ar*H*), 7.30 – 7.20 (3H, m, Ar*H*), 7.14 – 7.08 (2H, m, Ar*H*), 6.81 (1H, td, *J* = 7.4, 1.2 Hz, Ar*H*), 6.65 (1H, dd, *J* = 7.9, 1.2 Hz, Ar*H*), 5.15 (1H, app. dt, *J* = 5.6, 3.6 Hz, C*H*NO_2), 5.08 (1H, d, *J* = 3.1 Hz, C*H*Ar), 4.09 (1H, br. s, N*H*), 3.46 – 3.34 (2H, m, CH_2), 2.37 (3H, s, CH_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 143.6 (Ar*C*), 136.2 (Ar*C*), 135.1 (Ar*C*), 131.0 (Ar*C*H), 129.3 (Ar*C*H), 128.8 (Ar*C*H), 127.6 (Ar*C*H), 127.0 (Ar*C*H), 126.1 (Ar*C*H), 119.1 (Ar*C*H), 116.9 (Ar*C*), 114.9 (Ar*C*H), 81.8 (*C*HNO_2), 53.6 (C*H*Ar), 30.2 (*C*H_2), 19.3 (*C*H_3); m/z (EI) 268 (100%, $M^{+\cdot}$); HRMS calcd. for $C_{16}H_{14}N_2O_2$: 268.1212, found 268.1215.

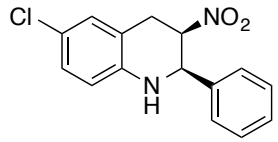
Ethyl (2*S**,3*R**)-3-nitro-1,2,3,4-tetrahydroquinoline-2-carboxylate **175l**



Prepared using general procedure **B**. Nitrostyrene **199l** (25.0 mg, 0.10 mmol) gave **175l** as a white solid (22 mg, 88%); mp 35 °C (dec); R_f = 0.41 (pet. Ether:DCM); IR ν_{max} (neat) 3386 (N-H), 1723 (C=O), 1555 (N-O) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.02 - 7.08 (2H, m, Ar*H*), 6.74 (1H, t, *J* = 7.4 Hz, Ar*H*), 6.64 (1H, d, *J* = 8.0 Hz, Ar*H*), 5.28-5.32 (1H, m, C*H*NO_2),

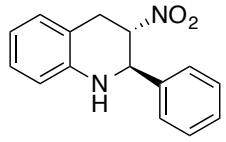
4.60 (1H, s, N*H*), 4.28-4.42 (3H, m, CH_2CH$_3$ & C*H*), 3.67 (1H, dd, *J* = 17.5, 3.2 Hz, CH*H*), 3.37 (1H, dd, *J* = 17.4, 5.2 Hz, C*H*H), 1.33 (3H, t, *J* = 7.2Hz, CH_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.9 (*C*=O), 141.5 (Ar*C*), 129.5 (Ar*C*H), 128.1 (Ar*C*H), 119.2 (Ar*C*H), 115.7 (Ar*C*), 115.2 (Ar*C*H), 78.5 (*C*HNO$_2$), 62.6 (*C*H$_2$), 55.6 (*C*HCOOEt), 30.4 (*C*H$_2$), 14.2 (*C*H$_3$); m/z (ESI+) 251 (100%, M+H$^+$); HRMS calcd. for $C_{12}H_{15}N_2O_4$: 251.1032, found 251.1037.

(2*R*,3*R*)-6-Chloro-3-nitro-2-phenyl-1,2,3,4-tetrahydroquinoline **175r**



Prepared using general procedure **B**. Nitrostyrene **199r** (34.0 mg, 0.12 mmol) gave **175r** as a yellow wax (32 mg, 93%); Enantiomeric excess 93%; R_f = 0.20 (9:1 pet. Ether:EtOAc); $[\alpha]_D^{20}$= 65.2 (c = 0.2, $CHCl_3$); IR ν_{max} (neat) 3385 (N-H), 1547 (N-O), 1368 (N-O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) 7.32-7.36 (3H, m, Ar*H*), 7.17-7.23 (2H, m, Ar*H*), 7.07-7.09 (2H, m, Ar*H*), 6.58-6.61 (1H, m, Ar*H*), 5.11 (1H, ddd, J = 7.8, 5.3, 4.0 Hz, C*H*NO$_2$), 5.05 (1H, d, *J* = 3.8 Hz, C*H*Ph), 4.41 (1H, br. s, N*H*), 3.28 (1H, dd, *J* = 16.9, 7.7 Hz, C*H*H), 3.22 (1H, dd, *J* = 16.8, 5.5 Hz, CH*H*); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 141.3 (Ar*C*), 137.8 (Ar*C*), 129.1 (Ar*C*H), 129.0 (Ar*C*H), 128.9 (Ar*C*H), 127.9 (Ar*C*H), 126.7 (Ar*C*H), 123.0 (Ar*C*), 117.6 (Ar*C*), 115.1 (Ar*C*H), 82.1 (*C*HNO$_2$), 57.1 (*C*HPh), 27.7 (*C*H$_2$); m/z (EI) 288 (100%, M$^{+\cdot}$); HRMS (CI) calcd. for $C_{15}H_{14}ClN_2O_2$: 288.0666, found 288.0660; HPLC analysis: Daicel Chiralpak OD, hexane/*iso*-propanol = 1:1, flow rate = 1.0 mL/min, λ = 254 nm, retention time 8.3 min (major) and 21.0 (minor).

(2*R*,3*S*)-3-Nitro-2-phenyl-1,2,3,4-tetrahydroquinoline **160a**



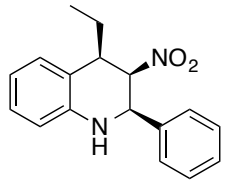
To a solution of *cis*-tetrahydroquinoline **175a** (24 mg, 0.10 mmol) in $CDCl_3$ (0.50 mL) was added DBU (15 µL, 0.10 mmol) and stirred for 18 h. The reaction mixture was concentrated *in vacuo* to give the crude tetrahydroquinoline **160a** as a red gum. Purification by column chromatography (9:1 Hexanes:EtOAc) gave the pure *trans*-tetrahydroquinoline **160a** as a yellow solid (18 mg, 72 %); mp 99-100 °C (Lit. 98-99 °C); R_f = 0.19 (9:1 pet. Ether:EtOAc) $[\alpha]_D^{20}$= 39.2 (c = 0.15, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.32 (5H, m, Ar*H*), 7.14 – 7.03 (2H, m, ArH), 6.75 (1H, t, *J* = 7.4, Ar*H*), 6.61 (1H, d, *J* = 7.9 Hz, Ar*H*), 4.98 – 4.83 (2H, m, C*H*), 3.58 (1H, dd, *J* = 16.2, 8.6 Hz, C*H*H), 3.25 (1H, dd, *J* = 16.1, 4.8 Hz, CH*H*); HPLC analysis: Daicel Chiralpak OD, hexane/*iso*-propanol = 1:1, flow rate = 1.0 mL/min, λ = 254 nm, retention time 15.9 min (major) and 28.2 (minor).
Data consistent with literature.[67]

5.9 Preparation of 4-alkyl-3-nitro-2-aryl-tetrahydroquinolines

General Procedure C

To a solution of **199** (0.25 mmol) and $Cu(OTf)_2$ (5 mol%) in Et_2O (2.5 mL) was added a solution of $ZnEt_2$ (0.375 mL of a 1.0 M solution in Hexanes, 1.5 equiv.) at -78 °C for up to 1 h and then stirred for up to 2 h at rt. The resulting suspension was re-cooled to -78 °C over 30 min and TFA (0.63 mmol, 2.5 equiv.) was added dropwise, stirred for up to 1 h and then stirred for up to 1 h at rt. The reaction was then quenched with sat. aq. $NaHCO_3$ (50 mL), the product was extracted with EtOAc (3 x 30 mL), the combined organic layers washed with brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give the crude tetrahydroquinoline **268**. Purification by column chromatography (1:1 Hexanes:DCM) gave the pure tetrahydroquinoline **269**.

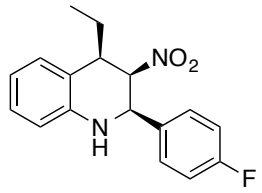
((2*R**,3*R**,4*R**)-4-Ethyl-3-nitro-2-phenyl-1,2,3,4-tetrahydroquinoline **268a**



Prepared using the general procedure **C**. Nitrostyrene **199a** (63 mg, 0.25 mmol) gave the crude tetrahydroquinoline **268a** as a light brown gum. Purification by column chromatography gave the pure tetrahydroquinoline **268a** as a brown oil (44 mg, 62%); R_f = 0.33 (1:1 DCM:Hexanes); IR ν_{max} (neat) 3416 (N-H), 1545 (N-O), 1368 (N-O) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.32-7.45 (5H, m, Ar*H*), 7.08-7.16 (2H, m, Ar*H*), 6.82 (1H, t, *J* = 7.5 Hz, Ar*H*), 6.68 (1H, dd, *J* = 7.9, 1.3 Hz, Ar*H*), 4.98 (1H, app. t, *J* = 2.9 Hz, C*H*NO_2), 4.76 (1H, d, *J* = 3.3 Hz, C*H*Ph), 4.25 (1H, br. s, N*H*), 3.20 (1H, ddd, *J* = 8.3, 5.3, 2.4 Hz, C*H*Et), 1.69 – 2.01 (2H, m, C$H_2$$CH_3$), 1.12 (3H, t, *J* = 7.4 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 142.5 (Ar*C*). 138.1 (Ar*C*), 129.4 (Ar*C*H), 129.1 (Ar*C*H), 129.1 (Ar*C*), 127.6 (Ar*C*H), 126.8 (Ar*C*H), 121.2 (Ar*C*H), 118.8 (Ar*C*H), 114.7 (Ar*C*H), 86.8 (*C*H), 54.6 (*C*H), 41.8 (*C*HEt), 30.7 (*C*$H_2$$CH_3$), 11.6 ($CH_2$*C*$H_3$); m/z (ESI+) 234

(100%, M-$H_3NO_2^+$), (45%, M+H^+); HRMS $C_{17}H_{19}N_2O_2$ calcd. 283.1447, found 283.1448.

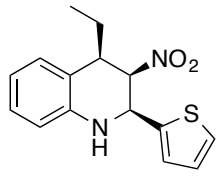
(2*R**,3*R**,4*R**)-4-Ethyl-2-(4-fluorophenyl)-3-nitro-1,2,3,4-tetrahydroquinoline **268b**



Prepared using the general procedure **C**. Nitrostyrene **199g** (90 mg, 0.33 mmol) gave the crude tetrahydroquinoline **268b** as an orange gum (9:1 *cis*,*cis*:*cis*,*trans*). Purification by column chromatography (7:3 DCM:Hexanes) gave the pure tetrahydroquinoline **268b** as a yellow wax (79 mg, 80%, 9:1 *cis*,*cis*:*cis*,*trans*); R_f = 0.30 (1:1 DCM:Hexanes); IR ν_{max} (neat) 3386 (N-H), 1546 (N-O), 1367 (N-O) cm^{-1}; ^{1}H NMR^{cis,cis} ($CDCl_3$, 600 MHz) δ 7.30 – 7.36 (2H, m, Ar*H*), 7.07 – 7.16 (4H, m, Ar*H*), 6.81 – 6.85 (1H, m, Ar*H*), 6.68 (1H, dd, *J* = 8.0, 1.1 Hz, Ar*H*), 4.94 (1H, dd, *J* = 3.3, 2.6 Hz, C*H*NO_2), 4.75 (1H, d, *J* = 3.3 Hz, C*H*Ar), 4.21 (1H, br. s, N*H*), 3.20 (1H, ddd, *J* = 8.3, 5.4, 2.6 Hz, C*H*Et), 1.73 – 1.97 (2H, m, C$H_2$$CH_3$), 1.12 (3H, t, *J* = 7.4 Hz, CH_2CH_3); ^{1}H NMR^{cis,trans} (600 MHz, $CDCl_3$) δ 7.38 (1H, dd, *J* = 8.7, 5.2 Hz, Ar*H*), 7.25 (1H, d, *J* = 8.1 Hz, Ar*H*), 6.65 (1H, dd, *J* = 7.9, 1.3 Hz, Ar*H*), 5.21 (1H, dd, *J* = 4.7, 2.9 Hz, C*H*NO_2), 4.85 (1H, d, *J* = 2.9 Hz, C*H*Ar), 3.33 (1H, app. dt, *J* = 10.1, 4.7 Hz, C*H*Et), 2.43 – 2.35 (1H, m, C*H*HCH_3), 1.50 – 1.44 (1H, m, CH*H*CH_3), 0.89 (3H, t, *J* = 7.0 Hz, CH_2CH_3), *remaining signals could not be resolved*; ^{13}C NMR^{cis,cis} ($CDCl_3$, 151 MHz) δ 163.0 (d, *J* = 248.1 Hz, Ar*C*F), 128.6 (d, *J* = 8.4 Hz, Ar*C*H), 142.3 (Ar*C*), 133.9 (d, *J* = 3.8 Hz, Ar*C*), 129.4 (Ar*C*H), 127.7 (Ar*C*H), 121.2 (Ar*C*H), 119.0 (Ar*C*), 116.1 (d, *J* = 21.7 Hz, Ar*C*H), 114.8 (Ar*C*H), 86.9 (*C*H), 54.0 (*C*H), 41.6 (*C*HEt), 30.6 (*C*$H_2$$CH_3$), 11.6 ($CH_2$*C*$H_3$); ^{1}H NMR^{cis,trans} (600 MHz, $CDCl_3$) δ 7.38 (1H, dd, *J* = 8.7, 5.2 Hz, Ar*H*), 7.25 (1H, d, *J* = 8.1 Hz, Ar*H*), 6.65 (1H, dd, *J* = 7.9, 1.3 Hz, Ar*H*), 5.21 (1H, dd, *J* = 4.7, 2.9 Hz, C*H*NO_2), 4.85 (1H, d, *J* = 2.9 Hz, C*H*Ar), 3.33 (1H, dt, *J* = 10.1, 4.7 Hz, C*H*Et), 2.43 – 2.35 (1H, m, C*H*HCH_3),1.47 (1H, ddt, *J* =

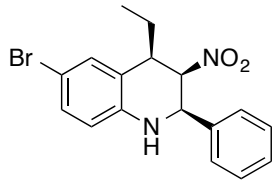
17.6, 14.1, 7.0 Hz, CH*H*CH_3), 0.89 (3H, t, *J* = 7.0 Hz, CH_2CH_3), *remaining signals could not be resolved*; ^{19}F NMR^{cis,cis} ($CDCl_3$, 282 MHz) δ -112.6 (1F, s, Ar*F*); ^{19}F NMR^{cis,trans} (282 MHz, $CDCl_3$) δ -112.6 (Ar*F*); m/z (ESI+) 301 (100%, $M+H^+$); HRMS $C_{17}H_{18}FN_2O_2$ calcd. 301.1352, found 301.1364.

(2*S**,3*R**,4*R**)-4-Ethyl-3-nitro-2-(thiophen-2-yl)-1,2,3,4-tetrahydroquinoline **268c**



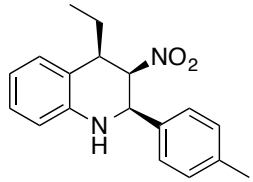
Prepared using the general procedure **C**. Nitrostyrene **199i** (26 mg, 0.10 mmol) gave the crude tetrahydroquinoline **268c** as a brown oil. Purification by column chromatography (1:1 Hexanes:DCM) gave the pure teterahydroquinoline **268c** as a brown oil (15 mg, 53%); R_f = 0.33 (1:1 DCM:Hexanes); IR ν_{max} (neat) 3400 (N-H), 1546 (N-O), 1364 (N-O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.26 – 7.28 (1H, m, Ar*H*), 7.04 – 7.16 (3H, m), 7.00 (1H, dd, *J* = 5.1, 3.6 Hz, Ar*H*), 6.85 (1H, td, *J* = 7.5, 1.2 Hz, Ar*H*), 6.68 (1H, dd, *J* = 7.9, 1.1 Hz, Ar*H*), 5.12 (1H, d, *J* = 3.6 Hz, C*H*Ar), 5.05 (1H, app. t, *J* = 3.9 Hz, C*H*NO_2), 3.37 (1H, app. dt, *J* = 8.5, 4.7 Hz, C*H*Et), 1.78 – 1.92 (2H, m, C*H*$_2$$CH_3$), 1.05 (3H, t, *J* = 7.4 Hz, CH_2C*H*$_3$); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 141.8 (Ar*C*), 140.4 (Ar*C*), 129.2 (Ar*C*H), 127.7 (Ar*C*H), 127.2 (Ar*C*H), 126.0 (Ar*C*H), 125.9 (Ar*C*H), 121.4 (Ar*C*), 119.6 (Ar*C*H), 115.4 (Ar*C*H), 86.6 (*C*H), 51.5 (*C*H), 40.7 (*C*HEt), 29.5 (*C*H_2CH_3), 11.0 (CH_2*C*H_3); m/z (ESI+) 301 (100%, $M+H^+$); HRMS $C_{15}H_{17}N_2O_2S$ calcd. 289.1011, found 289.1001.

(2*R**,3*R**,4*R**)-6-Bromo-4-ethyl-3-nitro-2-phenyl-1,2,3,4-tetrahydroquinoline **268d**



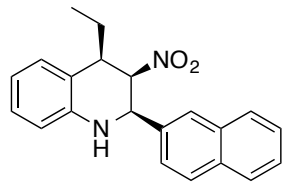
Prepared using the general procedure **C**. Nitrostyrene **199u** (83 mg, 0.25 mmol) gave the crude tetrahydroquinoline **268d** as a red oil (9:1 *cis*,*cis*:*cis*,*trans*). Purification by column chromatography (1:1 Hexanes:EtOAc) gave the pure tetrahydroquinoline **268d** as a yellow wax (72 mg, 80%, 9:1 *cis*,*cis*:*cis*,*trans*); R_f = 0.41 (9:1 pet. Ether:EtOAc); IR ν_{max} (neat) 3376 (N-H), 1540 (N-O), 1334 (N-O) cm^{-1}; ^1H NMR^{cis,cis} ($CDCl_3$, 600 MHz) δ 7.32 – 7.43 (5H, m, Ar*H*), 7.22 – 7.26 (1H, m, Ar*H*), 7.20 (1H, dd, *J* = 8.6, 2.2 Hz, Ar*H*), 6.57 (1H, d, *J* = 8.5 Hz, Ar*H*), 4.95 (1H, dd, *J* = 3.3, 2.3 Hz, C*H*NO_2), 4.73 (1H, d, *J* = 3.3 Hz, C*H*Ar), 4.28 (1H, br. s, N*H*), 3.16 (1H, ddd, *J* = 8.2, 5.3, 2.3 Hz, C*H*Et), 1.71 – 1.95 (2H, m, CH_2CH_3), 1.13 (3H, t, *J* = 7.4 Hz, CH_2CH_3); ^1H NMR^{cis,trans} (600 MHz, $CDCl_3$) δ 6.98 – 6.95 (1H, m, Ar*H*), 6.53 (1H, d, *J* = 8.5 Hz, Ar*H*), 5.22 (1H, dd, *J* = 4.6, 3.0 Hz, C*H*NO_2), 4.84 (1H, d, *J* = 3.0 Hz, C*H*Ph), 3.32 – 3.28 (1H, m, C*H*Et), 1.72 – 1.66 (1H, m, C*H*HCH_3), 1.50 – 1.43 (1H, m, CH*H*CH_3), 0.89 (3H, t, *J* = 7.1 Hz, CH_3), *remaining signals could not be resolved*; ^{13}C NMR^{cis,cis} ($CDCl_3$, 151 MHz) δ 141.6 (Ar*C*), 137.6 (Ar*C*), 131.9 (Ar*C*H), 130.4 (Ar*C*H), 129.3 (2x Ar*C*H), 126.7 (Ar*C*H), 123.3 (Ar*C*), 116.3 (Ar*C*), 86.3 (Ar*C*H), 79.7 (*C*H), 54.5 (*C*H), 41.7 (*C*HEt), 30.8 (*C*H_2CH_3), 11.6 (CH_2CH_3); m/z (ESI+) 361 (100%, $M+H^+$); HRMS $C_{17}H_{18}BrN_2O_2$ calcd. 361.0552, found 361.0565.

(2*R**,3*R**,4*R**)-4-Ethyl-3-nitro-2-(*p*-tolyl)-1,2,3,4-tetrahydroquinoline **268e**



Prepared using the general procedure **C**. Nitrostyrene **199c** (106 mg, 0.40 mmol) gave the crude tetrahydroquinoline **268e** as a brown oil. Purification by column chromatography (1:1 Hexanes:DCM) gave the pure tetrahydroquinoline **268e** as a cream wax (87 mg, 73%); R_f = 0.30 (9:1 pet. Ether:EtOAc); IR ν_{max} (neat) 3401 (N-H), 1542 (N-O), 1365 (N-O) cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.18 – 7.25 (4H, m, Ar*H*), 7.09 – 7.14 (2H, m, Ar*H*), 6.79-6.82 (1H, m, Ar*H*), 6.67 (1H, dd, *J* = 7.9, 1.2 Hz, Ar*H*), 4.94 (1H, dd, *J* = 3.3, 2.4 Hz, C*H*NO_2), 4.71 (1H, d, *J* = 3.3 Hz, C*H*Ar), 4.21 (1H, br. s, N*H*), 3.18 (1H, ddd, *J* = 8.2, 5.3, 2.5 Hz, C*H*Et), 2.36 (3H, s, ArCC*H*$_3$), 1.73 - 1.96 (2H, m, C*H*$_2$$CH_3$), 1.11 (3H, t, *J* = 7.4 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 142.6 (Ar*C*), 139.0 (Ar*C*), 135.0 (Ar*C*), 129.8 (Ar*C*H), 129.4 (Ar*C*H), 127.6 (Ar*C*H), 126.6 (Ar*C*H), 121.3 (Ar*C*), 118.7 (Ar*C*H), 114.7 (Ar*C*H), 86.9 (*C*HNO_2), 54.4 (*C*HAr), 41.8 (*C*HEt), 30.8 (*C*H_2CH_3), 21.3 (ArC*C*H_3), 11.6 (CH_2*C*H_3); m/z (EI) 220 (100%, M-$C_2H_6^+$), 296 (65%, M^+); HRMS $C_{18}H_{20}N_2O_2$ calcd. 296.1519, found 296.1520.

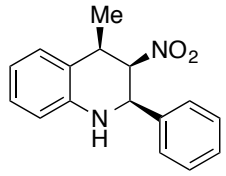
(2*R**,3*R**,4*R**)-4-Ethyl-3-nitro-2-(*p*-tolyl)-1,2,3,4-tetrahydroquinoline **268f**



Prepared using the general procedure **C**. Nitrostyrene **199j** (92 mg, 0.30 mmol) gave the crude tetrahydroquinoline **268f** as a brown oil. Purification by column chromatography (1:1 Hexanes:DCM) gave the pure tetrahydroquinoline **268f** as a brown oil (86 mg, 86%); R_f = 0.25 (9:1 pet. Ether:EtOAc); IR ν_{max} (neat) 3366 (N-H), 1539 (N-O), 1336 (N-O) cm^-

[1]; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.51 - 8.04 (6H, m, Ar*H*), 7.44 (1H, dd, *J* = 8.5, 1.8 Hz, Ar*H*), 7.13 – 7.18 (2H, m, Ar*H*), 6.85 - 6.74 (2H, m, ArH), 5.08 (1H, dd, *J* = 3.3, 2.4 Hz, C*H*NO_2), 4.92 (1H, d, *J* = 3.3 Hz, C*H*Ar), 4.36 (1H, br. s, N*H*), 3.25 (1H, ddd, *J* = 8.2, 5.4, 2.3 Hz, C*H*Et), 1.77 – 2.01 (2H, m, C$H_2$$CH_3$), 1.16 (3H, t, *J* = 7.4 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 134.3 (Ar*C*), 133.6 (Ar*C*), 133.4 (Ar*C*), 132.8 (Ar*C*), 129.2 (Ar*C*H), 129.2 (Ar*C*H), 129.0 (Ar*C*H), 128.3 (Ar*C*H), 128.2 (Ar*C*H), 127.9 (Ar*C*H), 127.6 (Ar*C*H), 127.2 (Ar*C*H), 126.7 (Ar*C*H), 126.7 (Ar*C*H), 126.0 (Ar*C*H), 124.3 (Ar*C*H), 122.9 (Ar*C*), 118.9 (Ar*C*H), 114.8 (Ar*C*H), 86.8 (*C*H), 54.7 (*C*H), 42.0 (*C*HEt), 30.9 (*C*$H_2$$CH_3$), 11.7 ($CH_2$*C*$H_3$); m/z (ESI+) 333 (100%, M+H^+); HRMS $C_{18}H_{21}N_2O_2$ calcd. 333.1603, found 333.1596.

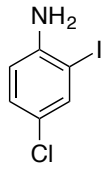
(2*R**,3*R**,4*R**)-4-Methyl-3-nitro-2-phenyl-1,2,3,4-tetrahydroquinoline **268g**



Prepared using the general procedure **C**. Nitrostyrene **199a** (101 mg, 0.40 mmol) gave the crude tetrahydroquinoline **268g** as a brown oil. Purification by column chromatography (1:1 Hexanes:DCM) gave the pure tetrahydroquinoline **268g** as a red oil (56 mg, 52%); R_f = 0.40 (9:1 pet. Ether:EtOAc); IR ν_{max} (neat) 3349 (N-H), 1544 (N-O), 1367 (N-O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.28 – 7.40 (5H, m, Ar*H*), 7.18 (1H, d, *J* = 7.7 Hz, Ar*H*), 7.12 (1H, m, Ar*H*), 6.83 (1H, td, *J* = 7.5, 1.2 Hz, Ar*H*), 6.67 (1H, dd, *J* = 8.0, 1.2 Hz, Ar*H*), 4.85 (1H, dd, *J* = 4.2, 3.6 Hz, C*H*NO_2), 4.82 (1H, d, *J* = 3.6 Hz, C*H*Ph), 3.45 (1H, qd, *J* = 7.1, 4.1 Hz, C*H*CH_3), 1.49 (3H, d, *J* = 7.1 Hz, CHCH_3); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 142.3 (Ar*C*), 138.1 (Ar*C*), 129.1 (Ar*C*H), 129.1 (Ar*C*H), 128.8 (Ar*C*H), 127.7 (Ar*C*H), 126.8 (Ar*C*H), 122.4 (Ar*C*), 119.0 (Ar*C*H), 114.7 (Ar*C*H), 89.6 (*C*HPh), 55.0 (*C*HNO_2), 33.6 (*C*HCH_3), 22.7 (CH*C*H_3); m/z (EI) 206 (100%, M-$CH_4NO_2^+$), 268 (65%, M^+); HRMS $C_{16}H_{16}N_2O_2$ calcd. 268.1206, found 268.1206.

5.10 Miscellaneous Compounds

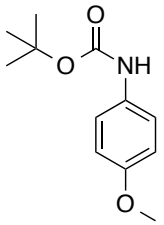
4-Chloro-2-iodoaniline **235b**



To a solution of 4-chloroaniline (3.84 g, 30.0 mmol) and $NaHCO_3$ (3.40 g, 44.0 mmol) in H_2O (21 mL) was added a solution of KI (5.00 g, 30.0 mmol), I_2 (7.60 g, 30.0 mmol) in H_2O (10 mL) over 45 min and then left to stir at rt for 3 h. The reaction mixture was added sat. $Na_2S_2O_3$ (100 mL), the product was extracted with DCM (3 x 50 mL), the combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude iodoaniline **235b** as a brown oil. Purification by column chromatography (7:3 Hexanes:Et_2O) gave the pure iodoaniline **235b** as a low melting brown solid (2.11 g, 28%); R_f = 0.28 (8:2 pet. Ether:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (1H, dd, *J* = 2.4, 0.8 Hz, Ar*H*), 7.10 (1H, dd, *J* = 8.5, 2.4 Hz, Ar*H*), 6.66 (1H, d, *J* = 8.5 Hz, Ar*H*), 4.08 (2H, br. s, NH_2).

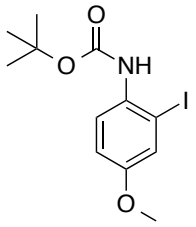
Data consistent with literature.[139]

Tert-butyl (4-methoxyphenyl)carbamate **328**



To a solution of *p*-anisidine (615 mg, 5.00 mmol) in EtOH (10 mL) was added Boc_2O (1.64 g, 7.50 mmol) and left to stir at rt for 1 h, the reaction mixture was then concentrated *in vacuo* to give the crude aniline **328** as a brown solid. Purification by column chromatography (85:15 pet. Ether:EtOAc) gave pure aniline **328** as a colourless oil (1.11 g, 100%); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.24 - 7.30 (2H, m, Ar*H*), 6.84 (2H, m, Ar*H*), 6.25 - 6.45 (1H, br. s, N*H*), 3.79 (3H, s, OCH_3), 1.52 (9H, s, CCH_3).
Data consistent with literature.[140]

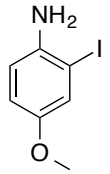
Tert-butyl (2-iodo-4-methoxyphenyl)carbamate **329**



To a solution of Boc-aniline **328** (555 mg, 2.48 mmol) in Et_2O (6 mL) was added a solution of *t*BuLi (1.60 M in pentane, 3.87 mL, 6.20 mmol) dropwise at -20 °C and then left to stir for 3 h. The solution was cooled to -78 °C and added a solution of diiodoethane (1.05 g, 3.72 mmol) in Et_2O (8 mL) dropwise then left to stir for 18 h at rt. The reaction mixture was added sat. $Na_2S_2O_3$ (50 mL), the product was extracted with Et_2O (3 x 50 mL), the combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude iodoaniline **329** as a brown oil. Purification by column chromatography (9:1 Hexanes:Et_2O) gave the pure iodoaniline **329** as a colourless wax (511 mg, 59%); R_f = 0.33 (8:2 pet. Ether:Et_2O); ^{1}H NMR ($CDCl_3$, 600 MHz) δ

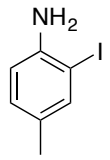
7.83 (1H, br. s, Ar*H*), 7.30 (1H, d, *J* = 3.0 Hz, Ar*H*), 6.90 (1H, dd, *J* = 9.0, 2.6 Hz, Ar*H*), 6.55 (1H, br. s, N*H*), 3.77 (3H, s, OCH_3), 1.53 (9H, s, CCH_3).
Data consistent with literature.

2-Iodo-4-methoxyaniline **235c**



A solution of Boc-aniline **329** (450 mg, 1.29 mmol) in DCM (10 mL) was added TFA (1.18 mL, 15.5 mmol) and left to stir at rt for 3 h. The reaction mixture was added 2N NaOH, then 2N HCl solution until pH 7. The product was extracted with DCM (3 x 10 mL), the combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give the crude iodoaniline **235c** as a brown oil. Purification by column chromatography (9:1 Hexanes:EtOAc) gave the pure iodoaniline **235c** as a brown oil (172 mg, 69%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (1H, d, *J* = 2.8 Hz, Ar*H*), 6.77 (1H, dd, *J* = 8.7, 2.8 Hz, Ar*H*), 6.70 (1H, d, *J* = 8.7 Hz, Ar*H*), 3.72 (3H, s, OCH_3).
Data consistent with literature.[140]

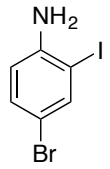
2-Iodo-4-methylaniline **235d**



To a solution of *p*-toluidine (2.14 g, 20.0 mmol) and $NaHCO_3$ (2.52 g, 30.0 mmol) in H_2O (25 mL) was added I_2 (5.08 g, 20.0 mmol) and left to stir at rt for 3 h. The reaction mixture was added $Na_2S_2O_3$ (50 mL), the product was extracted with DCM (3 x 30 mL), the combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give the crude iodoaniline **235d** as a brown oil.

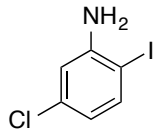
Purification by column chromatography (9:1 Hexanes:EtOAc) gave the pure iodoaniline **235d** as a brown oil (3.86 g, 83%), R_f = 0.40 (9:1 pet.Ether:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (1H, dd, *J* = 2.0, 0.9 Hz, Ar*H*), 6.95 (1H, ddd, *J* = 8.0, 2.0, 0.8 Hz, Ar*H*), 6.66 (1H, d, *J* = 8.1 Hz, Ar*H*), 3.87 (2H, br. s, NH_2), 2.21 (3H, s, CH_3).
Data in agreement with literature.[141]

4-Bromo-2-iodoaniline **235e**



To a solution of 2-iodoaniline (2.90 g, 17.6 mmol) in DCM (15 mL) was added NBS (2.47 g, 13.9 mmol) at 0 °C and stirred at rt for 5 h. The reaction mixture was diluted with brine (50 mL), the product extract with DCM (3 x 50 mL), the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give the crude iodoaniline **235e** as a brown solid. Purification by recrystallisation (Hexanes) gave the pure iodoaniline **235e** as brown needles (5.19 g, 99%); R_f = 0.35 (9:1 pet. Ether:EtOAc); mp 70-71 °C (Lit.[142] 70-71 °C); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 (1H, d, *J* = 2.2 Hz, Ar*H*), 7.22 (1H, dd, *J* = 8.5, 2.2 Hz, Ar*H*), 6.62 (1H, d, *J* = 8.6 Hz, Ar*H*), 4.11 (2H, br. s, NH_2).
Data consistent with literature.[142]

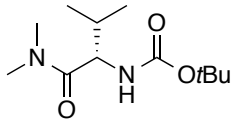
5-Chloro-2-iodoaniline **235f**



To s solution of 3-chloroaniline (3.00 g, 23.6 mmol) in AcOH (25 mL) was added NIS (5.60 g, 24.8 mmol) and then left to stir for at rt for 24 h. The reaction mixture was concentrated *in vacuo* to give the crude iodoaniline **235f** as a brown oil, purification by column chromatography (85:15

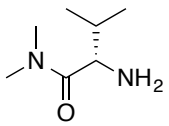
Hexanes:EtOAc) gave the pure iodoaniline **235f** as a grey solid (1.89 g, 32%); R_f = 0.38 (9:1 pet. Ether:EtOAc); mp 35-37 °C (Lit.[143] 40-42 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (1H, d, *J* = 8.5 Hz, Ar*H*), 6.80 (1H, d, *J* = 2.6 Hz, Ar*H*), 6.31 (1H, dd, *J* = 8.5, 2.6 Hz, Ar*H*), 3.85 – 3.64 (2H, br. s, NH_2).
Data in agreement with literature.[144]

Tert-butyl (*S*)-(1-(dimethylamino)-3-methyl-1-oxobutan-2-yl)carbamate **330**



To Boc-L-Valine (1.89 g, 8.70 mmol), EDC (1.83 g, 9.60 mmol), HOBt (1.29 g 9.60 mmol), dimethylamine hydrochloride (780 mg, 9.60 mmol) was added DCM (90 mL) and DIPEA (2.30 mL, 13.0 mmol) and left to stir for 12 h. The reaction mixture was diluted with Et_2O (200 mL), washed with 1N HCl (2 x 50 mL), sat. $NaHCO_3$ (100 mL) and brine (100 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to give the pure carbamate **330** as a colourless oil and on standing a white solid (1.93 g, 91%); mp 52-54 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.30 (1H, d, *J* = 8.5 Hz, N*H*), 4.46 (1H, dd, *J* = 9.3, 5.8 Hz, C*H*i*Pr*), 3.10 (3H, s, N(CH_3)$_2$), 2.97 (3H, s, N(CH_3)$_2$), 1.89 - 1.98 (1H, m, C*H*Me$_2$), 1.43 (9H, s, C(CH_3)$_3$), 0.96 (3H, d, *J* = 6.8 Hz, CH(CH_3)$_2$), 0.90 (3H, d, *J* = 6.8 Hz, CH(CH_3)$_2$).
Data is consistent with published data.[145]

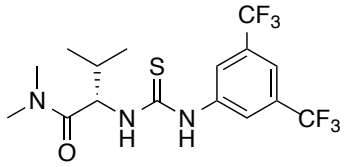
(*S*)-2-Amino-*N*,*N*,3-trimethylbutanamide **331**



A solution of TFA (30 mL) and (*S*)-*tert*-butyl (1-(dimethylamino)-3-methyl-1-oxobutan-2-yl)carbamate **330** (765 mg, 3.14 mmol) were stirred at 0 °C for 3 h, the solution was concentrated *in vacuo* and cooled to 0°C, 2.0 N

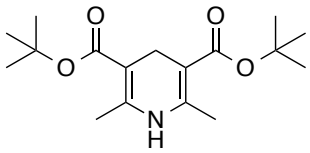
NaOH solution (40 mL) and 5% MeOH in DCM was added and stirred for 15 mins. The reaction mixture was extracted with 5% MeOH in DCM (3 x 20 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the pure amine **331** white solid (429 mg, 95%); mp 31-33 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.48 (1H, d, *J* = 5.3 Hz, C*H*i*P*r), 3.03 (3H, s, N(CH_3)$_2$), 2.97 (3H, s, N(CH_3)$_2$), 1.85 (1H, apt. oct, *J* = 6.6 Hz, C*H*Me$_2$), 1.70 (2H, br. s, NH_2), 0.96 (3H, dd, *J* = 6.9, 2.4 Hz, CH(CH_3)$_2$), 0.90 (3H, dd, *J* = 6.8, 2.5 Hz, CH(CH_3)$_2$).
Data is consistent with published data.[146]

(*S*)-2-(3-(3,5-Bis(trifluoromethyl)phenyl)thioureido)-*N*,*N*,3-trimethylbutanamide **71**



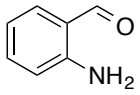
To a solution of 3,5-bis(trifluoromethyl)phenyl isothiocyanate (866 mg, 3.20 mmol) in DCM (15 mL) was added amine **331** (460 mg, 3.20 mmol) and left to stir for 72 h, the reaction mixture was then concentrated *in vacuo*. Purification by recrystallisation (hexanes) gave the pure thiourea **71** as a white solid (1.10 g, 83 %); mp 135-137 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.31 (1H, br. s, N*H*Ar), 8.40 (1H, d, *J* = 7.5 Hz, N*H*), 8.01 (2H, s, Ar*H*), 7.49 (1H, s, Ar*H*), 3.39 (3 H, s, N(CH_3)$_2$), 3.06 (3H, s, N(CH_3)$_2$), 2.08 (1H, app. oct, J = 7.0 Hz, C*H*(CH$_3$)$_2$), 1.13 (3 H, d, *J* = 6.8 Hz, CH(CH_3)$_2$), 1.09 (3 H, d, *J* = 6.8 Hz, CH(CH_3)$_2$).
Data is consistent with the published data.[33]

Di-*tert*-butyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate **68**



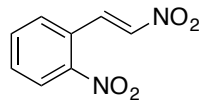
To a solution of ammonium acetate (6.17 g, 80.0 mmol) in EtOH (60 mL) was added *tert*-butylacetoacetate (6.50 mL, 40.0 mmol), formaldehyde (35 wt% in water, 1.60 mL, 20.0 mmol) and *para*-toluenesulfonic acid monohydrate (0.76 g, 4.00 mmol). The reaction mixture was heated to reflux for 1 h to give a yellow solution, which was left to cool to rt. The resulting suspension was filtered to give pure Hantzsch ester **68** as a yellow solid (5.56 g, 90 %); mp 148-149 °C (lit.[147] 151-153 °C); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 5.00 (1H, br. s, N*H*), 3.17 (2H, s, CH_2), 2.14 (6H, s, CH_3), 1.47 (18H, s, C(CH_3)$_3$).
Data consistent with literature.[148]

2-Aminobenzaldehyde **226**



To a solution of 2-nitrobenzaldehyde (10.6 g, 70.0 mmol) in EtOH (200 mL) and H_2O (50 mL) was added Fe (39.0 g, 700 mmol) and conc. HCl (583 µL, 7.00 mmol) and heated to 100 °C for 5 h. The reaction mixture was filtered through a pad of celite and concentrated to half volume *in vacuo*. The reaction mixture was diluted with brine (300 mL), the product was extracted with DCM (3 x 100 mL), the combined organic extracts washed with brine (300 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the pure aldehyde **226** as a yellow solid (7.07 g, 83%); mp 36-37 °C (lit. 39-40 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.85 (1H, s, C*H*O), 7.34 (2H, t, *J* = 7.7 Hz, Ar*H*), 6.95 (1H, t, *J* = 7.7 Hz, ArH), 6.79 (2H, d, *J* = 8.5 Hz, ArH), 3.66 (2H, br. s, NH_2).
Data in agreement with literature.[149]

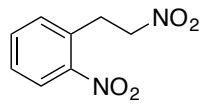
(*E*)-1-Nitro-2-(2-nitrovinyl)benzene **291**



A solution of 2-nitrobenzaldehyde (4.54 g, 30.0 mmol) and NH_4OAc (4.64 g, 30.0 mmol) in AcOH (60 mL) was stirred for 5 min, added $MeNO_2$ (mL, 120.0 mmol) and then stirred for 4 h at 100 °C. The reaction mixture was left to cool, added brine (600 mL), the product was extracted with DCM (3 x 300 mL), the combined organic extracts dried ($MgSO_4$) and concentrated *in vacuo* to give the crude nitrostyrene **291** as a brown solid. Purification by recrystallisation (EtOAc/pet. Ether) gave the pure nitrostyrene as a yellow solid (2.86 g, 49%); mp 102-104 °C (lit.[148] 101-102 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (1H, d, *J* = 13.5 Hz, C*H*), 8.21 (1H, dd, *J* = 7.9, 1.6 Hz, Ar*H*), 7.81 – 7.53 (3H, m, Ar*H*), 7.42 (1H, d, *J* = 13.5 Hz, C*H*).

Data consistent with literature.[150]

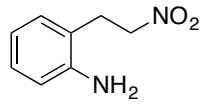
1-Nitro-2-(2-nitroethyl)benzene **332**



To a solution of nitrostyrene **291** (450 mg, 2.32 mmol) in MeOH (20 mL) was added $NaBH_4$ (264 mg, 6.96 mmol) portion wise and left to stir for 1 h. The reaction mixture was added brine (50 mL); the product was extracted with DCM (3 x 30 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude nitroalkane **332** as a light brown oil. Purification by column chromatography (6:4 pet. Ether:Et_2O) gave the pure nitroalkane **332** as a brown oil (387 mg, 85%); R_f = 0.45 (7:3 Hexanes:EtOAc); ^{1}H NMR ($CDCl_3$, 600 MHz) 8.09 (1H, dd, *J* = 8.3, 1.1 Hz, Ar*H*), 7.61 (1H, td, *J* = 7.5, 1.1 Hz, Ar*H*), 7.50 (1H, t, *J* = 8.5 Hz, Ar*H*), 7.41 (1H, dd, *J* = 7.7, 0.9 Hz, Ar*H*), 4.79 (2H, t, *J* = 6.8 Hz, C$H_2$$NO_2$), 3.62 (2H, t, *J* = 6.8 Hz, CH_2).

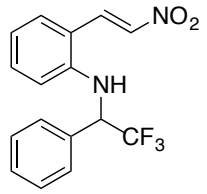
Data consistent with literature.[66]

2-(2-Nitroethyl)aniline **161**



A solution of nitroalkane **330** (149 mg, 0.76 mmol) in MeOH (7 mL) was added Pd/C (10 w/w, 7.5 mg) and stirred under an H_2 (g) balloon. The reaction mixture was filtered through a pad of celite (DCM wash) and concentrated *in vacuo* to give the crude aniline **161** as a yellow oil, which was used without further purification (121 mg, 96%); R_f = 0.33 (7:3 Hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (1H, td, *J* = 7.6, 1.6 Hz, Ar*H*), 7.06 – 7.01 (1H, m, Ar*H*), 6.81 – 6.66 (2H, m, Ar*H*), 4.63 (1H, t, *J* = 7.5 Hz, C*H*$_2$NO$_2$), 3.70 (1H, br. s, N*H*$_2$), 3.23 (1H, t, J = 7.5 Hz, C*H*$_2$). Data consistent with literature.[66]

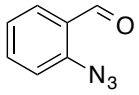
(*E*)-2-(2-Nitrovinyl)-*N*-(2,2,2-trifluoro-1-phenylethyl)aniline **259**



To a solution of nitrostyrene **240a** (40 mg, 0.13 mmol) in THF (1 mL) was added a solution of $LiBHEt_3$ (1.0 M in THF, 150 µL, 0.15 mmol) dropwise at -78 °C and then left to stir for 30 min. The reaction mixture was added TFA (14 µL, 0.188 mmol) and stirred for 15 min and then stirred for 30 min at rt. The reaction mixture was added sat. $NaHCO_3$ (50 mL), the product was extracted with EtOAc (3 x 50 mL), the combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give the crude amine **259** as a brown oil. Purification by column chromatography (9:1 Pentane:EtOAc) to give the pure amine **259** as a yellow oil (36 mg, 89%); R_f = 0.40 (9:1 pet. Ether:EtOAc); IR ν_{max} (neat) 3383 (N-H), 1579 (N-O), 1336 (N-O), 1167 (CF_3), 1123 (CF_3) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.23 (1H, d, *J* = 13.4 Hz, C*H*), 7.59 (1H, d, *J* = 13.4 Hz, C*H*), 7.48 – 7.36 (5H, m, Ar*H*),

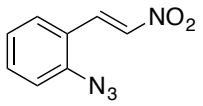
7.30 – 7.24 (2H, m, Ar*H*), 6.87 (1H, t, *J* = 7.5 Hz, Ar*H*), 6.67 (1H, d, *J* = 8.3 Hz, Ar*H*), 4.98 (1H, q, *J* = 6.7 Hz, C*H*NH), 4.55 (1H, br. s, N*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 145.1 (Ar*C*), 137.8 (Ar*C*H), 134.4 (*C*H), 133.5 (Ar*C*H), 133.0 (Ar*C*), 129.7 (Ar*C*H), 129.5 (*C*H), 129.3 (Ar*C*H), 127.9 (Ar*C*H), 124.8 (q, *J* = 282.0 Hz, *C*F_3), 120.4 (Ar*C*H), 117.6 (Ar*C*), 114.6 (Ar*C*H), 60.8 (q, *J* = 30.1 Hz, CHCF3); ^{19}F NMR (282 MHz, $CDCl_3$) δ -73.81 (3F, s, C*F*$_3$); m/z (ESI+) 323 (100%, M+H$^+$); HRMS $C_{14}H_{15}N_2O_2$ calcd. 323.1002, found 323.1009.

2-Azidobenzaldehyde **225**



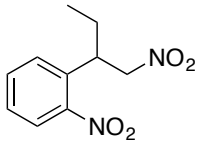
To a solution of 2-nitrobenzaldehyde (2.50 g, 16.0 mmol) in HMPA (40 mL) was added NaN_3 (2.70 g, 33.5 mmol) at 0 °C, the reaction mixture was then stirred for 24 h at rt. The reaction mixture was added MTBE (120 mL), poured over ice and the product was washed with brine (100 mL), the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give the crude azide **225** as a yellow oil. Purification by column chromatography (9:1 pet. Ether:Et_2O) gave the pure azide **225** as a yellow solid (2.18 g, 93%); R_f = 0.53 (8:2 pet.Ether:Et_2O); ^{1}H NMR ($CDCl_3$, 400 MHz) 10.36 (1H, s, C*H*O), 7.90 (1H, d, *J* = 7.8 Hz, Ar*H*), 7.66-7.60 (1H, m, Ar*H*), 7.30 (1H, d, *J* = 8.0 Hz, Ar*H*), 7.25 (1H, s, Ar*H*).
Data consistent with literature.[151]

(*E*)-1-Azido-2-(2-nitrovinyl)benzene **224**



To a solution of aldehyde **225** (1.00g, 6.80 mmol) in $MeNO_2$ (750 µL) was added a solution of KOH (470 mg, 7.50 mmol) in EtOH (20 mL) and then left to stir for 24 h. The reaction mixture was diluted with brine (30 mL), the product was extracted with DCM (3 x 20 mL), the combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude nitroalcohol as a brown oil. The crude nitroalcohol (850 mg, 4.10 mmol) was added Ac_2O (8.10 mL) and pyridine (810 µL) and left to stir for 24 h. The reaction mixture was diluted with brine (70 mL), the product was extracted with DCM (3 x 30 mL), the combined organic extracts were washed with brine (70 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude nitrostyrene **224** as a brown oil. Purification by column chromatography (8:2 pet.Ether:EtOAc) gave the pure nitrostyrene **224** as a yellow solid (450 mg, 58%); R_f = 0.40 (8:2 pet. Ether:Et_2O); mp 85-86 °C (lit.[149] 84 °C); ^{1}H NMR ($CDCl_3$, 500 MHz) 8.16 (1H, d, *J* = 13.5 Hz, C*H*), 7.77 (1H, d, *J* = 13.5 Hz, C*H*), 7.55-7.48 (2H, m, Ar*H*), 7.28-7.16 (2H, m, Ar*H*).
Data consistent with literature. [151]

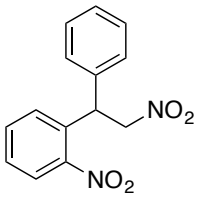
1-Nitro-2-(1-nitrobutan-2-yl)benzene **294**



A solution of nitrostyrene **291** (1.47 g, 7.58 mmol) and $Cu(OTf)_2$ (274 mg, 0.76 mmol, 10 mol%) in PhMe (8 mL) was cooled to -78 °C over 30 min. The reaction mixture was added diethylzinc (1.0 M in hexanes, 22.7 mL, 22.7 mmol) dropwise and left to stir for 30 min and then 1 h at rt. The reaction mixture was quenched with sat. NH_4Cl (100 mL), the product was extracted with EtOAc (3 x 75 mL), the combined organic extracts

washed with brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give the crude nitroalkane **294** as a brown oil. Purification by column chromatography (8:2 Hexanes:EtOAc) gave the pure nitroalkane **294** as a brown oil (289 mg, 17%); R_f = 0.34 (8:2 pet. Ether:EtOAc); IR ν_{max} (neat) 2968 (C-H), 1546 (N-O), 1519 (N-O), 1356 (N-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.85 – 7.82 (1H, m, Ar*H*), 7.63 – 7.58 (1H, m, Ar*H*), 7.45 – 7.37 (2H, m, Ar*H*), 4.71 (1H, dd, *J* = 12.8, 7.7 Hz, CH*H*), 4.65 (1H, dd, *J* = 12.9, 6.7 Hz, C*H*H), 4.06 – 3.95 (1H, m, C*H*), 1.90 – 1.77 (2H, m, CH_2), 0.89 (3H, t, *J* = 7.4 Hz, CH_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 150.8 (Ar*C*), 133.9 (Ar*C*), 133.2 (Ar*C*H), 128.5 (Ar*C*H), 128.2 (Ar*C*H), 125.0 (Ar*C*H), 79.5 (CH_2NO_2), 39.7 (*C*H), 25.8 (CH_2), 11.6 (CH_3); m/z (ESI+) 242 (100%, $M+NH_4^+$); HRMS $C_{10}H_{16}N_3O_4$ calcd. 242.1135, found 242.1136.

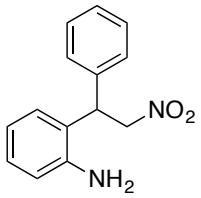
1-Nitro-2-(2-nitro-1-phenylethyl)benzene **295**



A solution of $Pd(TFA)_2$ (25.0 mg, 0.075 mmol, 5 mol%), bipyridine (17.6 mg, 0.113 mmol, 7.5 mol%) in MeOH (3 mL) was left to stir for 45 min. The reaction mixture was added phenylboronic acid (275 mg, 2.25 mmol), nitrostyrene **291** (291 mg, 1.50 mmol) and MeOH (3 mL) and then heated for 48 h at 40 °C. The reaction mixture was concentrated *in vacuo* to give the crude nitroalkane **295** as a brown oil. Purification by column chromatography (8:2 Hexanes:EtOAc) gave the pure nitroalkane **295** as an orange oil (366 mg, 90%); ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 – 7.94 (1H, m, Ar*H*), 7.60 (1H, t, *J* = 7.6 Hz, Ar*H*), 7.44 (2H, dd, *J* = 9.7, 7.8 Hz, Ar*H*), 7.27 – 7.39 (3H, m, Ar*H*), 5.65 (1H, t, *J* = 8.0 Hz, ArPhC*H*), 5.11 (1H, dd, *J* = 13.8, 8.0 Hz, CH*H*NO_2), 5.00 (1H, dd, *J* = 13.7, 8.0 Hz, C*H*HNO_2).

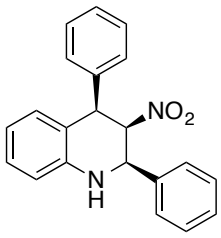
Data in agreement with literature.[152]

2-(2-Nitro-1-phenylethyl)aniline **298**



To a solution of nitroalkane **295** (272 mg, 1.00 mmol) in MeOH (3 mL) was added Pd/C (10% w/w, 13 mg, 10 mol%) and stirred under an H_2 (g) balloon for 90 min. The reaction mixture was filtered through a pad of celite (DCM wash) and concentrated *in vacuo* to give the crude aniline **298** as a yellow/orange gum. Purification by column chromatography (1:1 Hexanes:DCM) gave the pure aniline **298** as a yellow oil (79 mg, 33%); R_f = 0.13 (1:1 DCM:Hexanes); IR ν_{max} (neat) 3443 (N-H), 1549 (N-O), 1377 (N-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.33 – 7.36 (1H, m, Ar*H*), 7.27 – 7.30 (1H, m, Ar*H*), 7.24 – 7.26 (2H, m, Ar*H*), 7.13 (1H, td, *J* = 7.7, 1.5 Hz, Ar*H*), 7.07 (1H, dd, *J* = 7.7, 1.4 Hz, Ar*H*), 6.83 (1H, td, *J* = 7.5, 1.3 Hz, Ar*H*), 6.70 (1H, dd, *J* = 7.9, 1.2 Hz, Ar*H*), 5.07 (1H, dd, *J* = 12.4, 7.0 Hz, CH*H*NO_2), 4.86 – 4.98 (2H, m, C*H*HNO_2 & C*H*PhAr), 3.55 (2H, br. s, NH_2); ^{13}C NMR (151 MHz, $CDCl_3$) δ 144.3 (Ar*C*), 138.2 (Ar*C*), 129.4 (Ar*C*H), 128.7 (Ar*C*H), 128.1 (Ar*C*H), 128.0 (Ar*C*H), 126.9 (Ar*C*H), 124.1 (Ar*C*), 119.4 (Ar*C*H), 117.4 (Ar*C*H), 78.6 (*C*H_2NO_2), 44.2 (*C*H); m/z (ESI+) 243 (100%, $M+H^+$); HRMS $C_{14}H_{15}N_2O_2$ calcd. 243.1128, found 243.1130.

(2*R**,3*R**,4*R**)-3-Nitro-2,4-diphenyl-1,2,3,4-tetrahydroquinoline **296**



To a solution of aniline **298** (121 mg, 0.50 mmol) in DCM (1 mL) was added Na_2SO_4 (1.00 g) and then PhCHO (53.0 mg, 0.50 mmol) and then stirred for 24 hours. The reaction mixture was filtered and concentrated *in vacuo* to give the crude imine**.** The reaction mixture was redissolved in

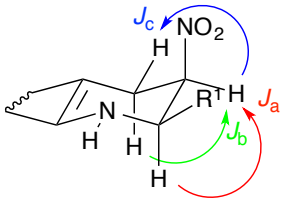
THF (2 mL) was cooled to -78 °C over 30 min, LiHMDS (600 µL, 0.60 M, 1.0 M in THF) was added dropwise and the reaction was left to stir for 15 min, the reaction mixture was then stirred for 30 min at rt. The reaction mixture was recooled to -78° C over 30 min, TFA (115 µL, 1.50 mmol) was added dropwise and left to stir for 30 min at -78 °C and then 30 min at rt. The reaction mixture was added sat. $NaHCO_3$ (70 mL), the product was extracted with DCM (3 x 25 mL), the combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give the crude tetrahydroquinoline **296** as a brown oil. Purification by column chromatography (1:1 Hexanes:DCM) gave the pure tetrahydroquinoline **296** as a brown oil (69 mg, 42%); IR ν_{max} (neat) 3397 (N-H), 1545 (N-O), 1364 (N-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.27 – 7.36 (6H, m, Ar*H*), 7.13 – 7.21 (5H, m, Ar*H*), 6.80 – 6.83 (1H, m, Ar*H*), 6.72 – 6.75 (2H, m, Ar*H*), 5.19 (1H, dd, *J* = 5.9, 3.8 Hz, C*H*), 4.88 (1H, dd, *J* = 3.9, 2.1 Hz, C*H*), 4.62 (1H, d, *J* = 5.9 Hz, C*H*), 4.45 (1H, br. s, N*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 143.1 (Ar*C*), 142.0 (Ar*C*), 138.1, (Ar*C*) 130.7 (Ar*C*H), 129.5 (Ar*C*H), 129.1 (Ar*C*H), 129.0 (Ar*C*H), 129.0 (Ar*C*H), 128.2 (Ar*C*H), 127.7 (Ar*C*H), 126.8 (Ar*C*H), 119.6 (Ar*C*), 119.0 (Ar*C*H), 114.4 (Ar*C*H), 89.8 (*C*HNO_2), 55.2 (*C*H), 44.8 (*C*H); m/z (ESI+) 341 (100%, $M+H^+$); HRMS $C_{14}H_{15}N_2O_2$ calcd. 341.1441, found 341.1443.

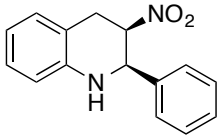
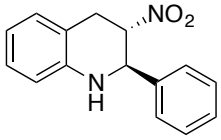
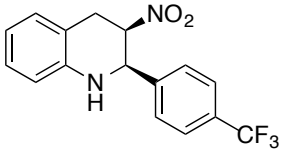
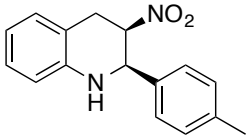
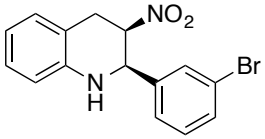
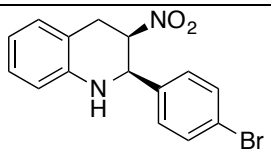
6.0 Appendices

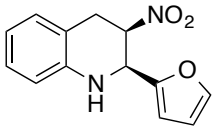
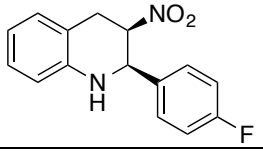
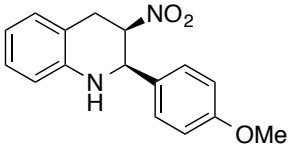
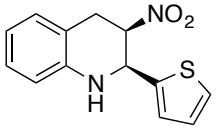
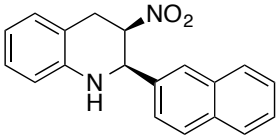
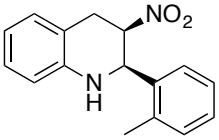
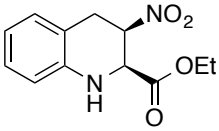
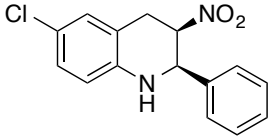
6.1 Table of Coupling Constants for Tetrahydroquinolines

The following tables list the structures and the ^{1}H NMR coupling constants of disubstitued-tetrahydroquinolines (Table 14) or trisubstituted-tetrahydroquinolines (Table 15). As previously described, typically the *cis*-diastereomer ^{3}J = ~ 2-4 Hz, while the *trans*-diastereomer ^{3}J = ~8 Hz. The coupling constants were taken as an average of the two values, unless only one could be visible.

Table 14: Table of coupling constants for *cis*-tetrahydroquinoline **175**.

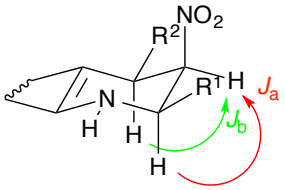


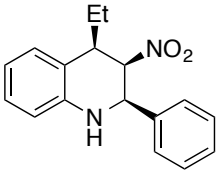
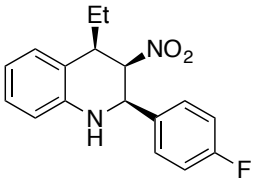
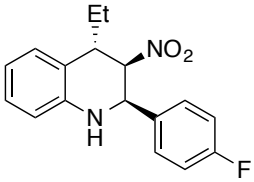
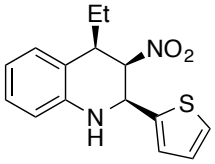
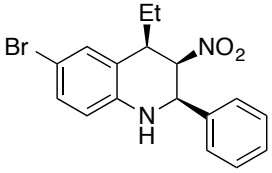
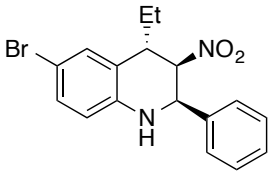
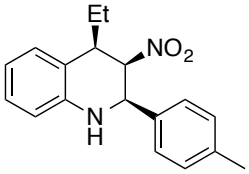
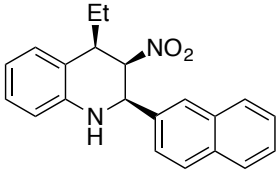
Tetrahydroquinoline	Name	J_a	J_b	J_c
	**175a**	4.1	8.5	5.4
	**160a**	7.5	8.6	4.8
	**175b**	4.2	7.6	6.5
	**175c**	4.2	8.4	5.3
	**175d**	4.1	8.1	5.5
	**175e**	4.8	8.4	5.5

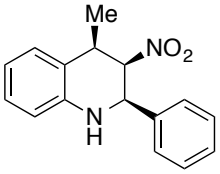
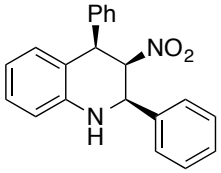
	**175f**	4.0	9.5	5.6
	**175g**	4.3	8.2	5.3
	**175h**	4.3	8.7	5.2
	**175i**	4.2	10.2	5.5
	**175j**	4.0	8.0	5.2
	**175k**	2.5	5.5	3.6
	**175l**	3.9	5.2	3.2
	**175r**	4.0	7.9	5.5

[a] *J*-values are given as an average of the two values unless only one could be determined

Table 15: Table of coupling constants for *cis*,*cis*-tetrahydroquinoline **268**.



Tetrahydroquinoline	Name	J_a[a]	J_b[a]
	**268a**	3.3	2.6
	**268b$_{major}$**	2.6	3.3
	**268b$_{minor}$**	2.9	4.7
	**268c**	3.8	4.3
	**268d$_{major}$**	3.3	2.3
	**268d$_{minor}$**	3.0	4.6
	**268e**	3.3	2.4
	**268f**	3.3	2.4

	**268g**	3.6	4.2
	**296**	3.9	5.8

[a] *J*-values are given as an average of the two values unless only one could be determined

Part 2: Towards the Synthesis of Schizozygine

1.0 Introduction

1.1 Isolation and Structural Determination

The Schizozygane alkaloids (Figure 1) are a group of hexacyclic alkaloids, which have been known for more than 5 decades. These alkaloids have been isolated from the east-African shrub *Schizozygia coffaeoides*, a plant that has been used as a traditional medicine for fungal and bacterial skin diseases.[153] The extracts from this plant have been shown to have high antifungal and antimicrobial activities and the principal component of the extract has been shown to be Schizozygine **1**, other components include Isoschizogaline **2** and Isoschigamine **3**.[154] When biological studies of the components were carried out, the MIC of Schizozygine **1** against a variety of fungi was found to be >500 μg/mL and it had no antimicrobial activity up to 500 μg/mL.[155]

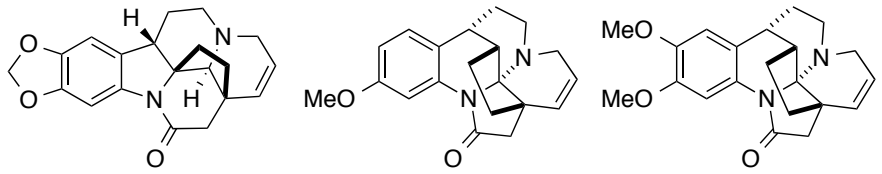
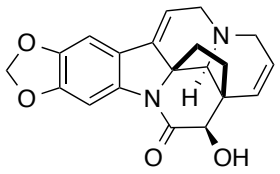


Figure 1: Two principle components of the *Schizozygia* extract.

These alkaloids have been extensively studied by ^{1}H NMR, vibrational circular dichroism (VCD) and electronic circular dichroism (ECD), and some stereochemical revisions have been reported.[156] The structure of Isoschizogamine **3** was confirmed by a racemic total synthesis by Heathcock *et al*.[157] and then the absolute stereochemistry by an asymmetric total synthesis by Fukuyama *et al*.[158] The structure of Schizozygine **1** has been proposed by Hájíček *et al*. through their detailed studies, but the structure remains unconfirmed. It has been found that less abundant alkaloids sharing the same central structure are potent antimicrobial and antifungal agents; the α–hydroxyl group is thought to be key for their activity (Figure 2).[155]

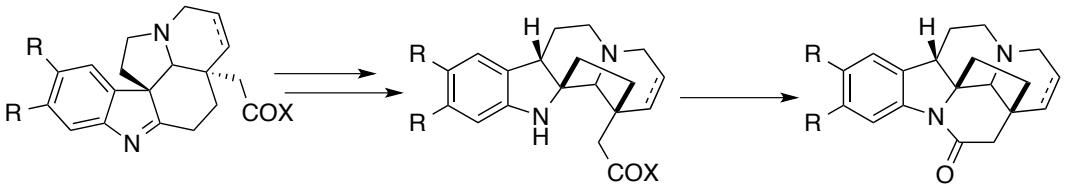


4

Figure 2: New Schizozygine-like alkaloid with potent antimicrobial and antibacterial activities.

1.2 Biosynthetic Hypothesis

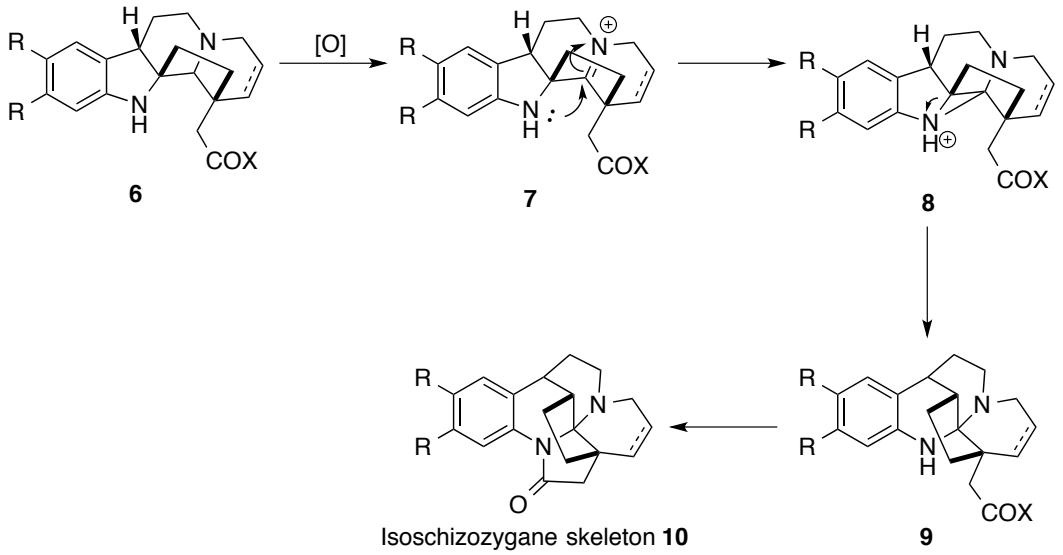
The biosynthetic origins of the Schizozygane alkaloids are thought to derive from the aspidosperma type alkaloids.[159] This biosynthetic origin was proposed by Hájíček. The aspidosperma skeleton **5** is thought to undergo an acid catalysed reductive rearrangement to intermediate **6** and then intramolecular lactamisation to the Schizozygane skeleton **7** (Scheme 1).



aspidospera skeleton **5** **6** Schizozygane skeleton **7**

Scheme 1: Proposed biosynthetic origin of Schizoygane skeleton from the aspidosperma alkaloid skeleton.

The Isoschizozygane skeleton can be made from intermediate **6** by oxidation to give iminium **7**, attack of the indoline nitrogen to give aziridinium **8** and then a reductive opening to give the skeleton **9**. Intramolecular lactamisation gives the Isoschizoygane core **10** (Scheme 2).



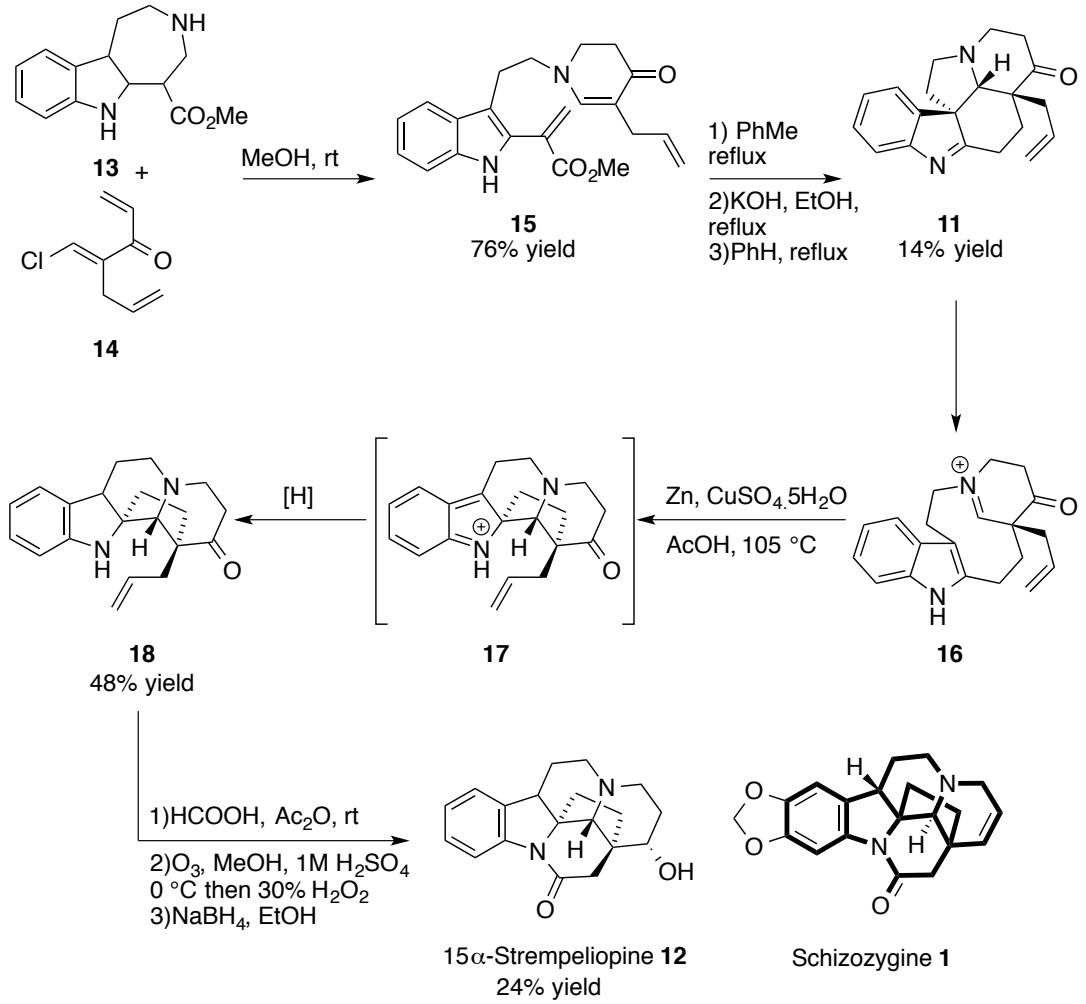
Scheme 2: Proposed conversion of intermediate **6** to isoschizoygane skeleton **10**.

1.3 Total Synthesis of Schizozygane Alkaloids

The Schizozygane and Isoschizozygane alkaloids have been the focus of a few total syntheses in the past. Their antimicrobial and antifungal activity makes them potentially useful for medicinal chemistry; they also contain a caged hexacyclic core that makes them an interesting target for synthetic chemists.

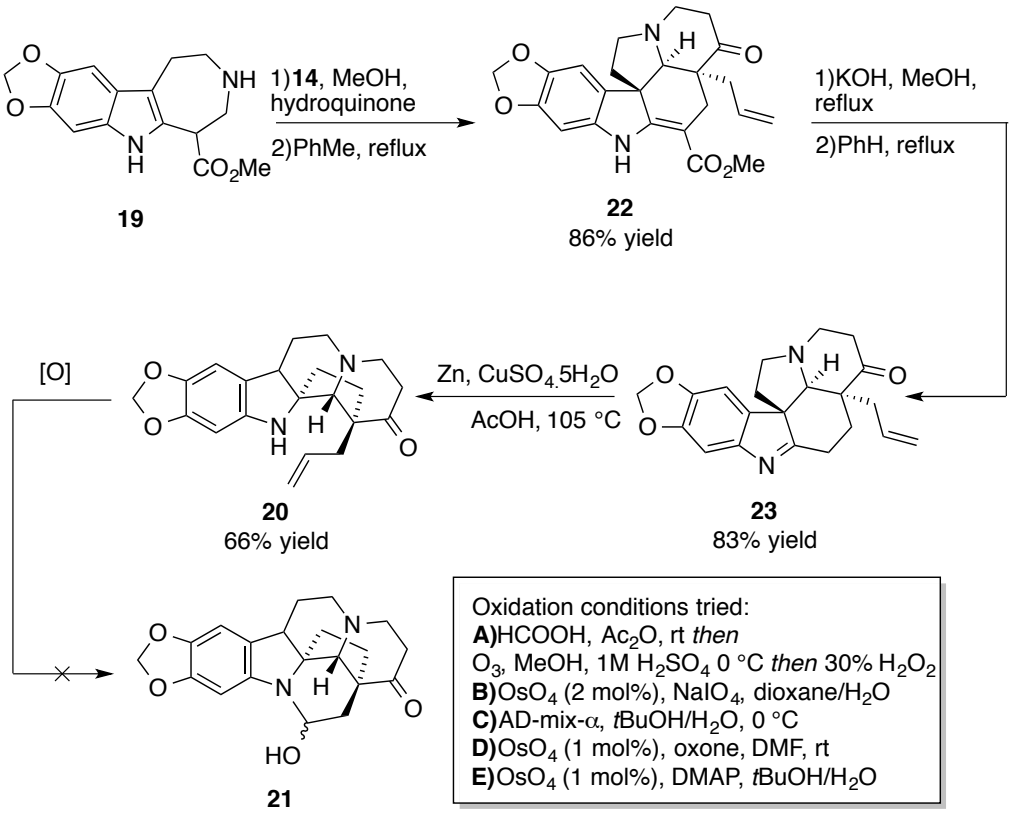
1.4 Attempted Total Synthesis of Schizozygine

The synthesis of Schizozygine **1** has been proposed by Hájíček *et al.* Their retrosynthesis relied on a reductive rearrangement of indolenine **11**. This rearrangement approach was successful for the total synthesis of 15a-hydroxystrempeliopine **12**; they used this as a model system for Schizozygine (Scheme 3). Their final step was to try to eliminate the pendant alcohol to install the double bond found in Schizozygine **1**. Tosylation of the alcohol **12** proceeded smoothly but elimination failed to provide the desired alkene.



Scheme 3: Total synthesis of 15α-Stremepelopoline **12**.

Since this report Hájíček *et al.* have begun applying their synthetic model to the total synthesis of (±)-Schizozygine **1** (Scheme 4). Their synthesis begins with the similar tryptamine derivative **19**, following a similar cycloaddition and then reductive rearrangement step to give the secoschizozygane **20** in a good yield. With secoschizozygane **20** at hand they attempted to ozonize the allyl fragment to give the hemiaminal **21**. Unfortunately when ozonolysis was attempted all they observed were decomposition products that they described as a black tar; dihydroxylation/oxidative cleavage did not form the desired hemiaminal **21** either, despite extensive investigations.[160]

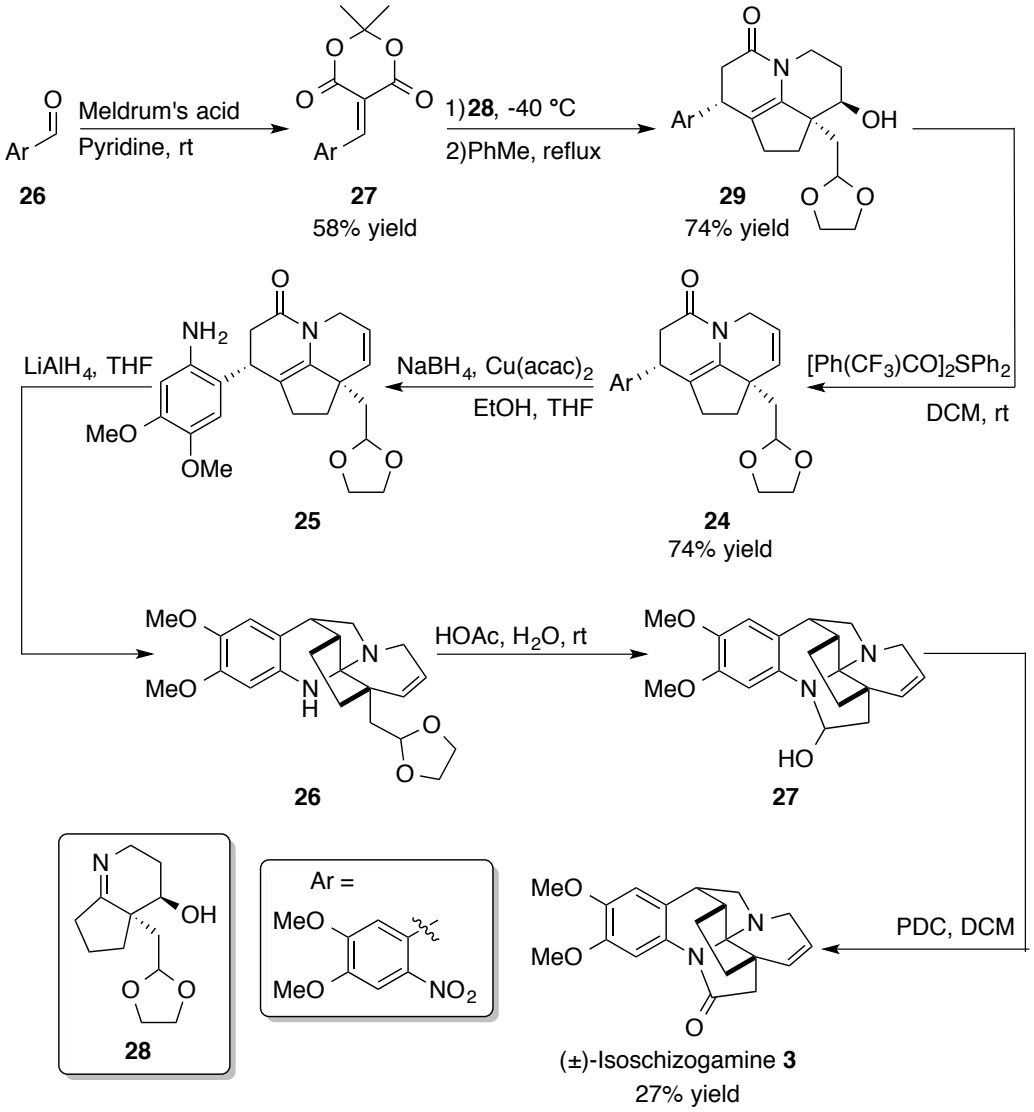


Scheme 4: Attempted synthesis of Schizozygine **1** by a reductive rearrangement strategy.

There are very few reports of other groups attempting the synthesis of Schizozygine or similar alkaloids, Padwa *et al*. have reported the synthesis of a similar alkaloid. Strempeliopine[161] and Saxton *et al*. had attempted to make Strempeliopine[162] from a Vinca alkaloid analogue they had previously made.[163]

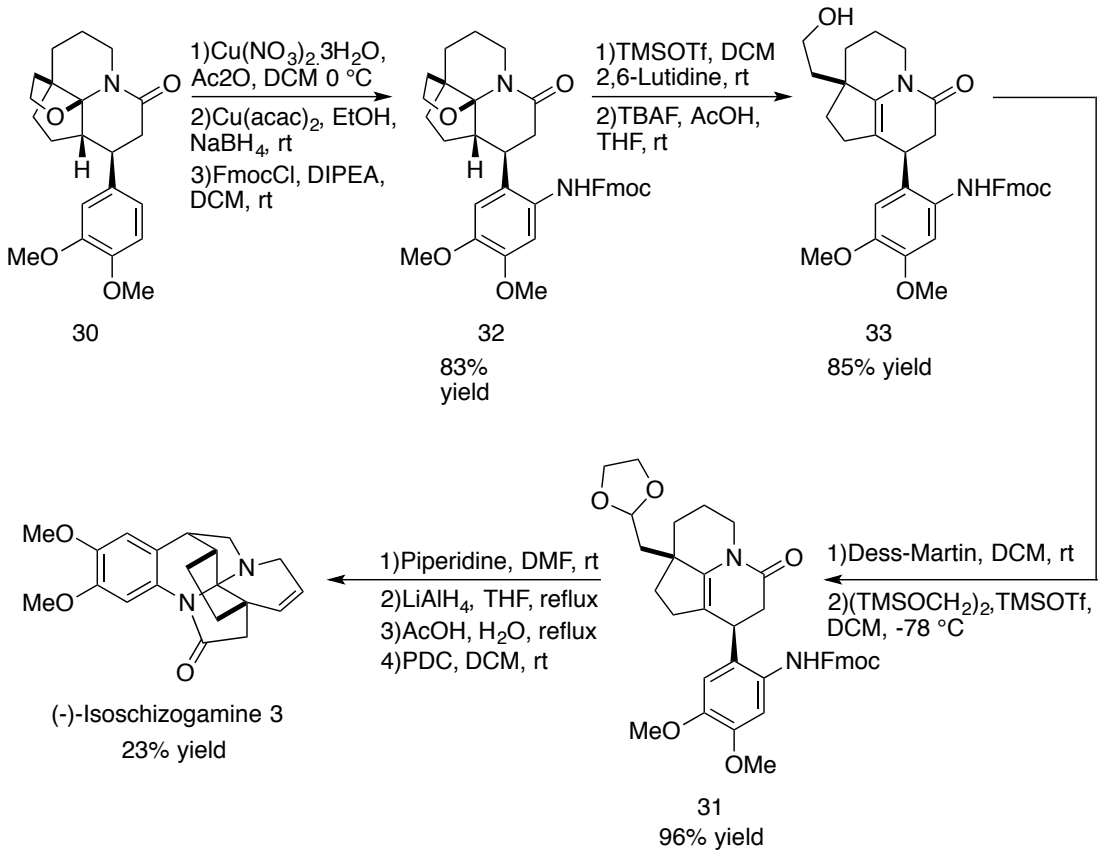
1.5 Isoschizogamine

The Isoschizozygane family of alkaloids have found a lot more interest in the total synthesis community, with many inventive approaches published. Heathcock *et al*. reported the first total synthesis of (±)-Isoschizagime **3** and this provides the benchmark for other total syntheses of this alkaloid family (Scheme 5).[157] Key steps in their retrosynthesis were very similar to their seminal biomimetic synthesis of Vallesamidine[164] They first build up the main carbon skeleton by creating the lactam **24** and then after reduction of the nitro group to amine **25** and deprotection of acetal **26** they get the hemiaminal intermediate **27**. Simple PCC oxidation of the hemiaminal provides racemic Isoschizogamine **3** efficiently. The key racemic bicyclic lactam **28** was made efficiently in 4 steps from the 2-substituted cyclopentanone.



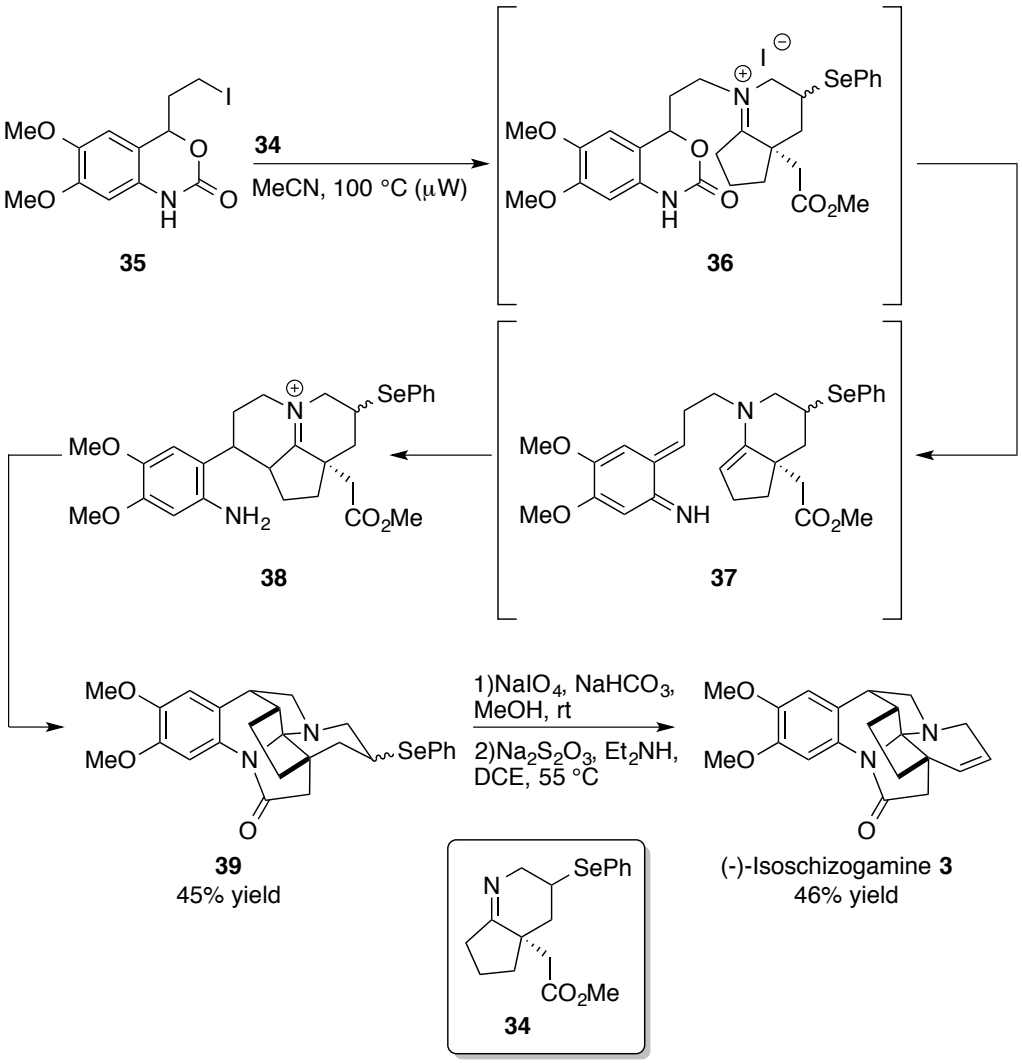
Scheme 5: First racemic total synthesis of Isoschizogamine.

Fukuyama *et al*. described the first asymmetric total synthesis of Isoschizogamine **3**. They first synthesised the key carbon framework **30** from (+)-*exo*-norborneol in 13 steps. They continued the synthesis by elaborating around this skeleton to give the enantioenriched Heathcock-like intermediate **31** (Scheme 6). Their final end game involved the same deprotection/hemiaminalisation/oxidation sequence that Heathcock had described. Comparison of the VCD, ECD and optical rotation data unambiguously confirmed the absolute configuration of Isochizogamine.[158]



Scheme 6: First asymmetric total synthesis of Isoschizogamine **3**.

More recently Zhu *et al*. reported their own approach to the total synthesis of (-)-Iscoschizogamine **3**. Their strategy deviated from most previous reports as it did not rely on the Heathcock intermediate **25**, but imine **34** is structurally very similar to imine **28** and so shares some similarities (Scheme 7). The domino sequence described by Zhu *et al*. also is similar to the approach described by Heathcock *et al*.



Scheme 7: Asymmetric synthesis of Isoschizozygine **3** by a novel domino sequence.

This synthesis provides a rapid and concise enantioselective route to Isoschizogamine **3** in 7 steps as the longest linear sequence with an overall yield of 11.3%.[165]

Other novel syntheses and studies towards the synthesis of Isoschizozygine **3** have been reported by Magomedov *et al*.,[166] Qin *et al*.[71] and Padwa *et al*.[167] and have provided insightful disconnections to this family of alkaloids.

1.6 Nitro Group in Total Synthesis

Nitroalkanes are an important C_1 synthon and hence is used in a variety of retrosyntheses to natural and unnatural products.[96] A key reason for the use of the nitro group is its use as a 'chemical chameleon';[168] the nitro group can be efficiently converted to the ketone by the Nef reaction,[169] reduced to the amine or radically denitrated (Figure 3).[96]

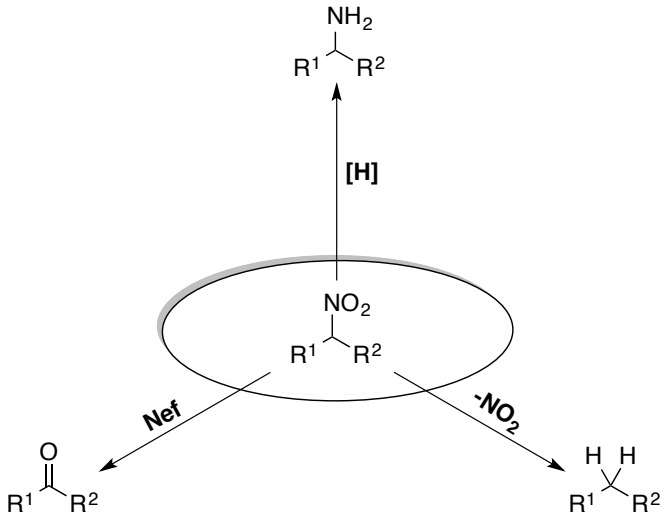
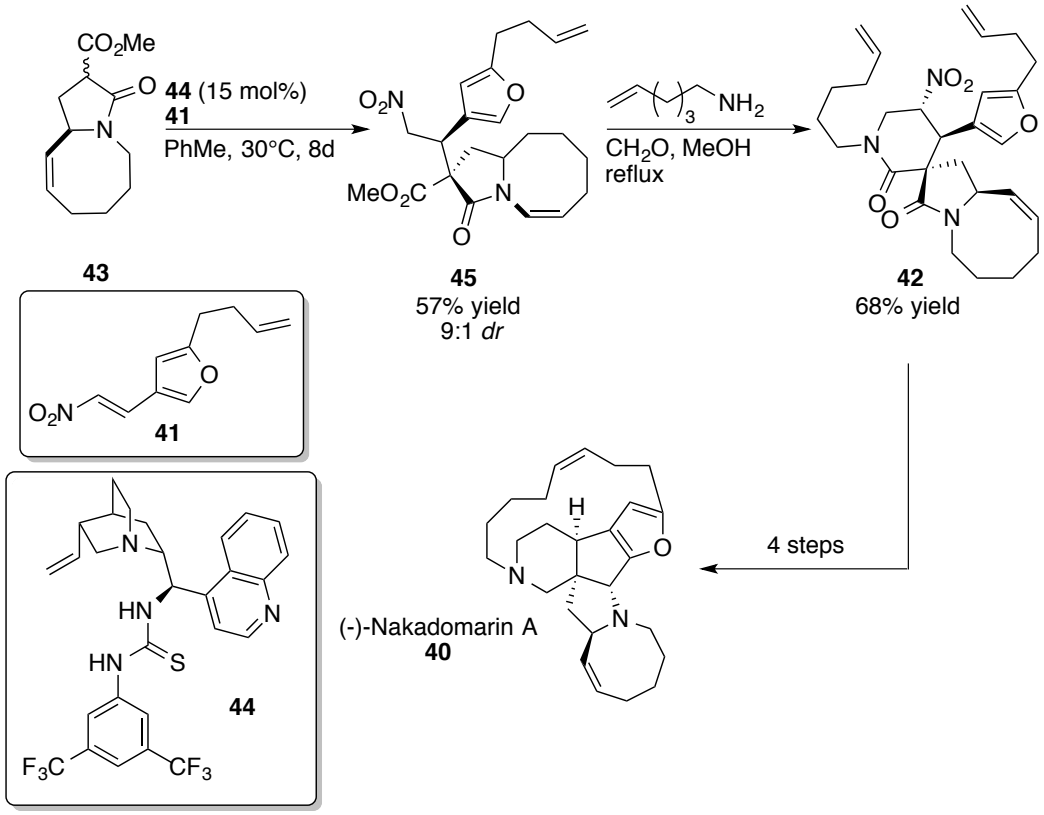


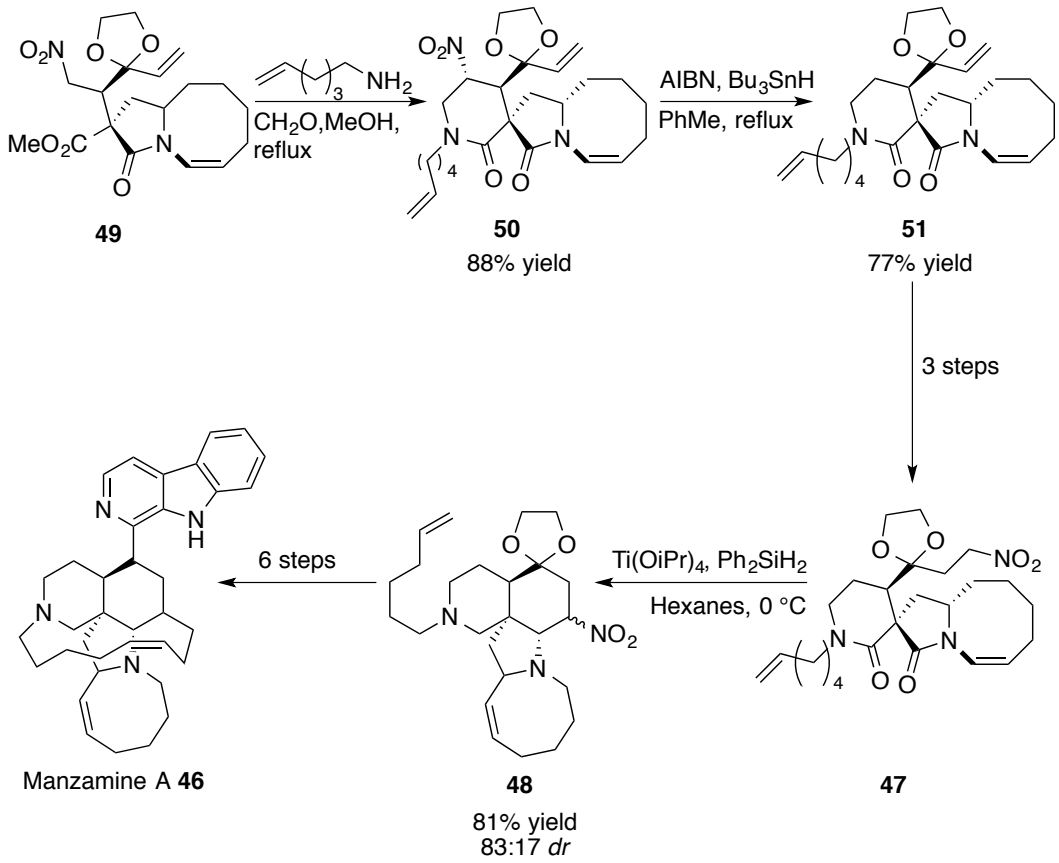
Figure 3: Synthetic transformations of the nitro group, relevant to total synthesis.

A nitro group and the nitro-Mannich reaction were used in the asymmetric total synthesis of Nakadomarin A **40** by Dixon *et al*. They used an organocatalytic Michael addition to nitrostyrene **41** and a nitro-Mannich reaction as key steps to create their optically enriched fragment **42** (Scheme 8).[60]



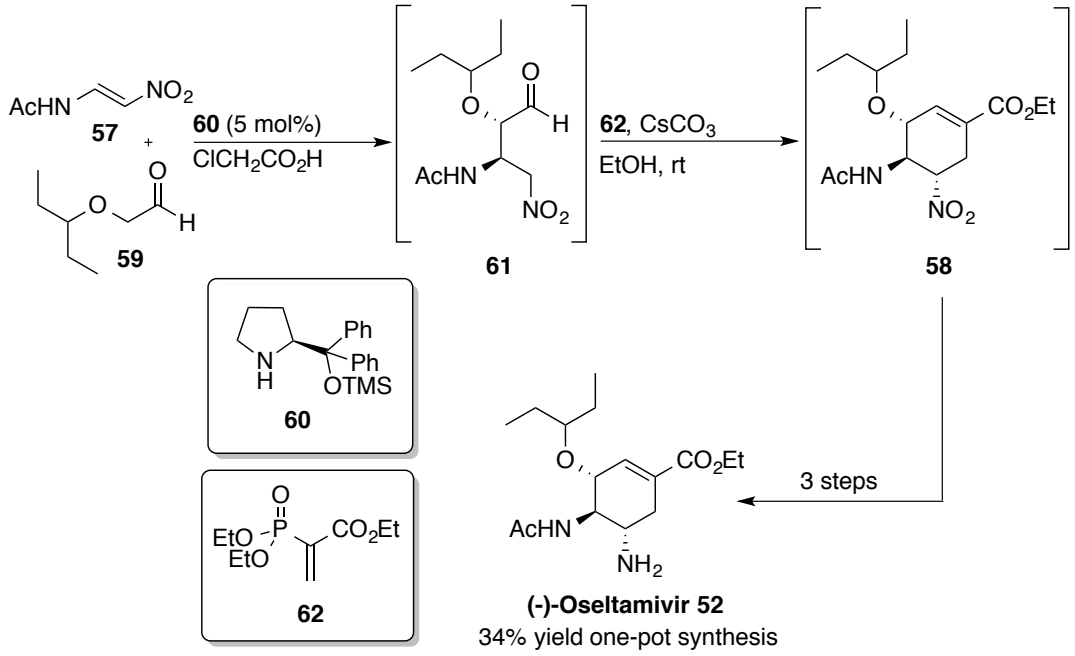
Scheme 8: Dixon's synthesis of (-)-Nakadomarin A **40**.

Using a similar approach as above, Dixon *et al*. later described the total synthesis of Manzamine A **46** and related alkaloids.[61] This used two nitro-Mannich reactions; the same nitro-Mannich/lactamisation strategy as above and then a reductive nitro-Mannich cyclisation, whereby amide **47** was converted to the iminium *in situ* and then cyclisation occurs to give **48** (Scheme 9). This method was used as inspiration for their iridium catalyzed reductive nitro-Mannich methodology.[53] They later removed the nitro group by radical denitration using $SnBu_3H$/AIBN again.



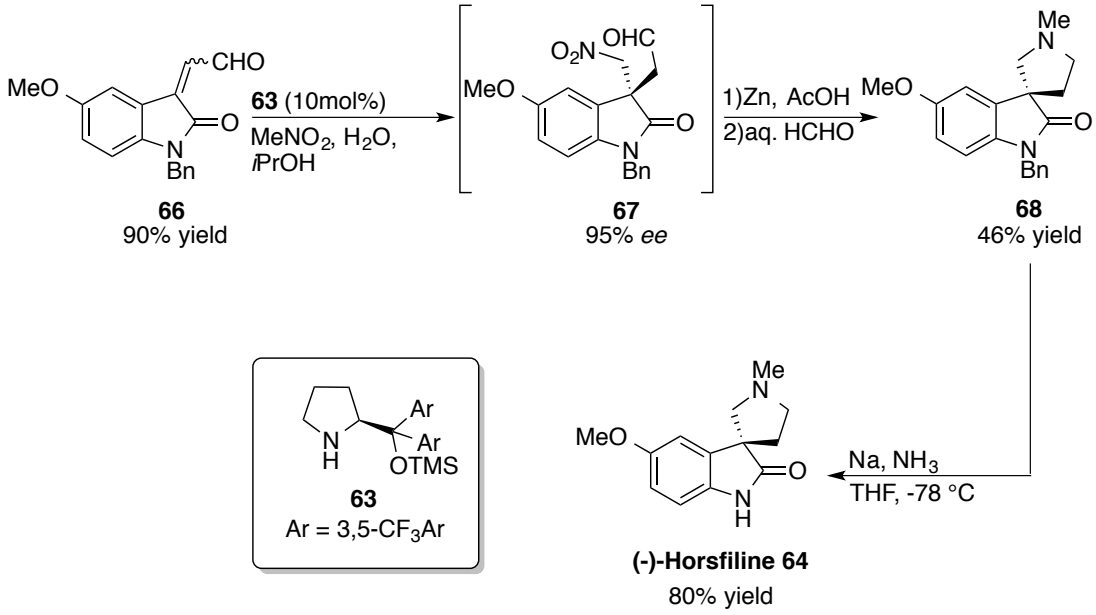
Scheme 9: Reductive cyclisation in the Manzamine A **46** synthesis.

Hayashi *et al*. have demonstrated the power and versatility of the nitro group by synthesizing multiple natural and unnatural products using the nitro group in key steps. Targets have included (-)-oseltamivir (Tamiflu) **52**,[170] ABT-341 **53**,[171] prostaglandin E_1 methyl ester **54**,[172] (-)-horsfilin **55**[173] and (s)-ethosuximide **56**.[174] The synthesis of (-)-oseltamivir (Tamiflu) **52** by Hayashi *et al*. demonstrates the highly efficient and impressive power of modern organic chemistry. From nitroalkene **57** Hayashi *et al*. managed to construct the densely functionalised enantioenriched carbocycle **58** through sequential one-pot addition of reagents. After this they performed various functional group manipulations, including the reduction of the nitro group to amine to furnish the desired product **52** in an overall yield of 34% (Scheme 10).[170]



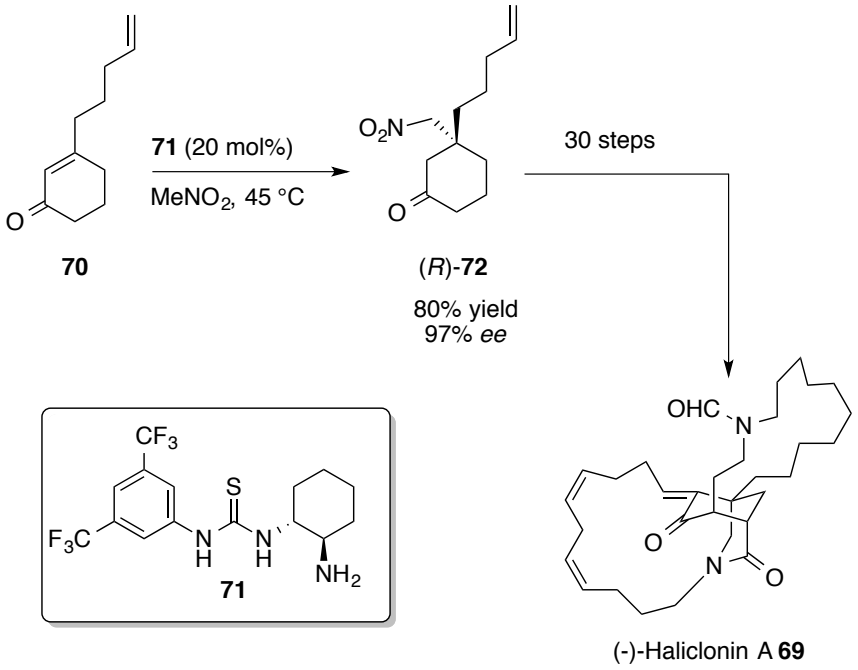
Scheme 10: Total synthesis of Oseltamavir **52**.

A similar strategy involving prolinol catalyst **63** and one-pot sequences was used by Hayashi *et al*. in the total synthesis of both (-)-Horsfilline **64** and (-)-Coerulescine **65** (Scheme 11). This synthesis demonstrates the important role nitromethane has in organic synthesis, as both a C_1 synthon and as a masked amine.[173]



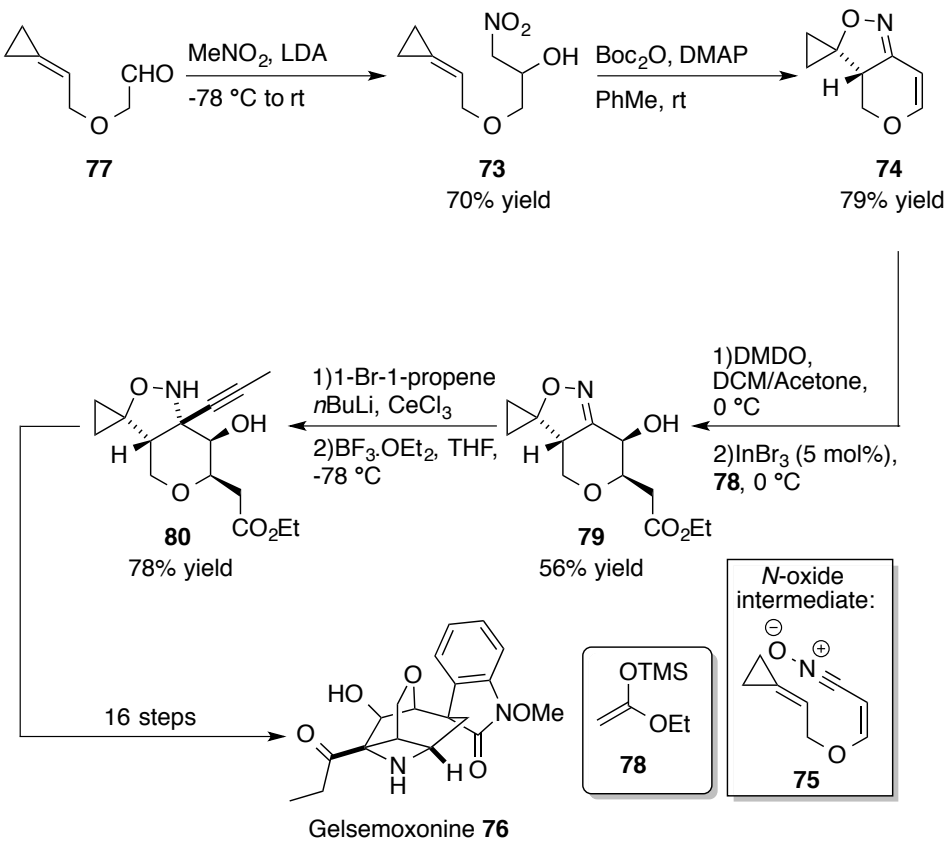
Scheme 11: Total synthesis of (-)-Horsfilline **64**.

An organocatalytic asymmetric synthesis of the complex macrocyclic alkaloid (-)-Haliclonin A **69** was reported by Huang *et al*.[175] Their retrosynthesis relied on building an all carbon quaternary stereocenter with high enantioselectivity. They achieved this by a thiourea-catalyzed addition of nitromethane to the α,β-unsaturated ketone **70**. This methodology used the cheap and readily available thiourea **71** and provided them with their key intermediate **72** in a high yield and enantioselectivity (Scheme 12). They later reduced this nitro group to the amine early in their synthesis.



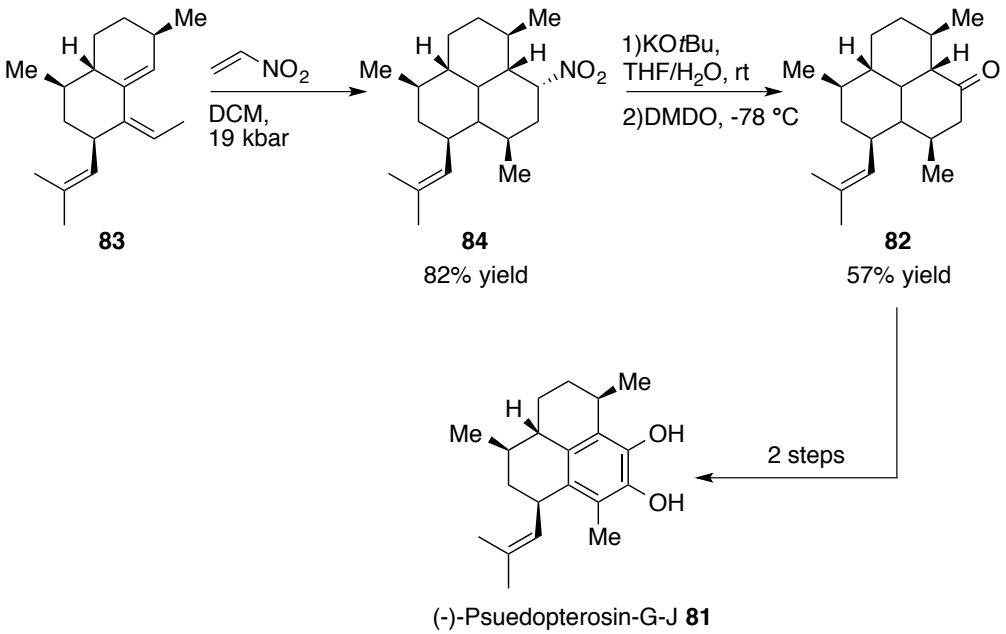
Scheme 12: Synthesis of ketone **72** bearing an all carbon quaternary stereocenter.

Another useful transformation of a nitro group is to an *N*-oxide; these can then be used in 1,3-dipolar cycloadditions. Carreira *et al*. converted the nitroalcohol **73** to the spiro-isoxazoline **74** via the *N*-oxide **75** (Scheme 13). This isoxazoline **74** was a key intermediate for their total synthesis of the alkaloid Gelsemoxonine **76**.[176]



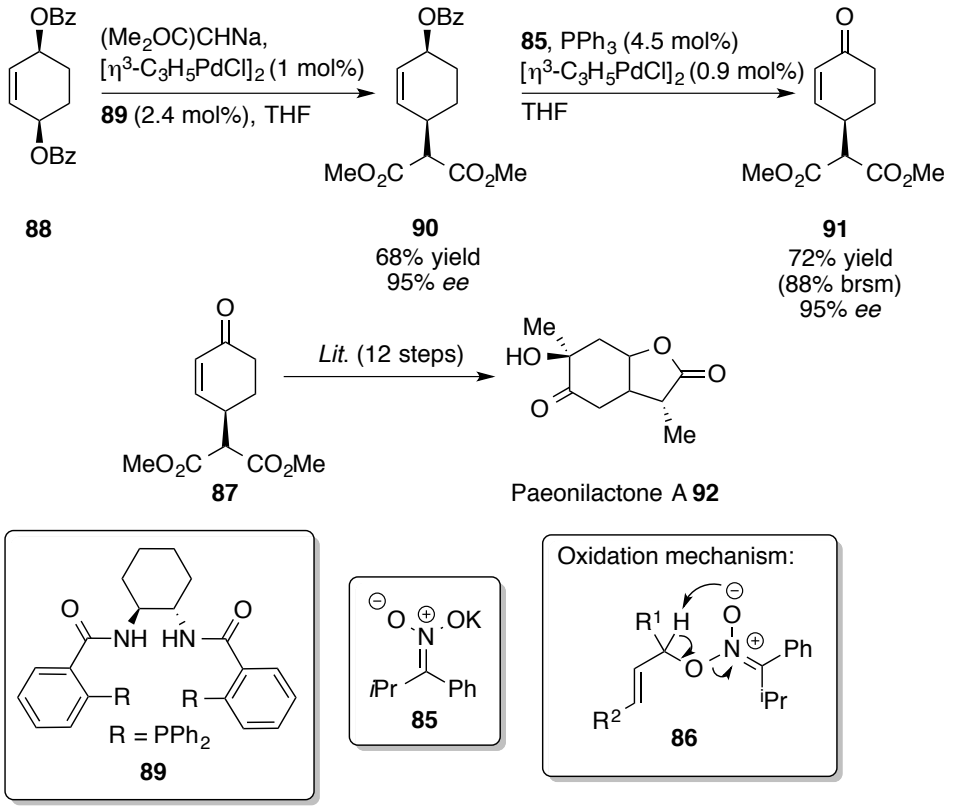
Scheme 13: Synthesis of Oxazoline **74** by a 1,3 dipole cycloaddition and its application to Gelsemoxonine **76**.

The enantioselective total synthesis of Pseudopterosin **81** by Sherburn *et al*. used the nitro group effectively on two occasions during their synthesis. They first built their tricyclic framework by a Diels-Alder reaction using nitroethylene and then used a Nef reaction to give the ketone **82**. Overall they used nitroethylene as a ketene equivalent (Scheme 14).[177]



Scheme 14: Use of nitroethylene as a ketene equivalent in the total synthesos of Psuedopterosin **81**.

A tangential use of the nitro group is the use of a nitronate as an oxidant, not a synthon. Trost *et al*. described the bulky nitronate **85** as a reagent in the enantioselective oxidation of allylic esters and carbonates.[178] The reaction is thought to proceed by *O*-alkylation of nitronate and then pericyclic fragmentation of intermediate **86** to give the ketone and oxime. In this report they then applied this chemistry to make Bäckvall's Paeonilactone A intermediate **87** (Scheme 15).[179] Using a nitronate as an oxidant represents a particularly novel and inventive use of the nitro group in organic synthesis, demonstrating its versatility.

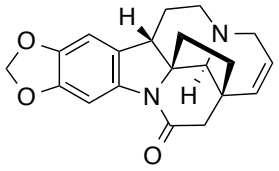


Scheme 15: Enantioselective allylic oxidation using **85** and its application to a formal synthesis of Paeonilactone A.

As highlighted, the versatility of the nitro group and its use in stereoselective synthesis makes the nitro group a very valuable tool in complex molecule synthesis.

2.0 Proposed Research

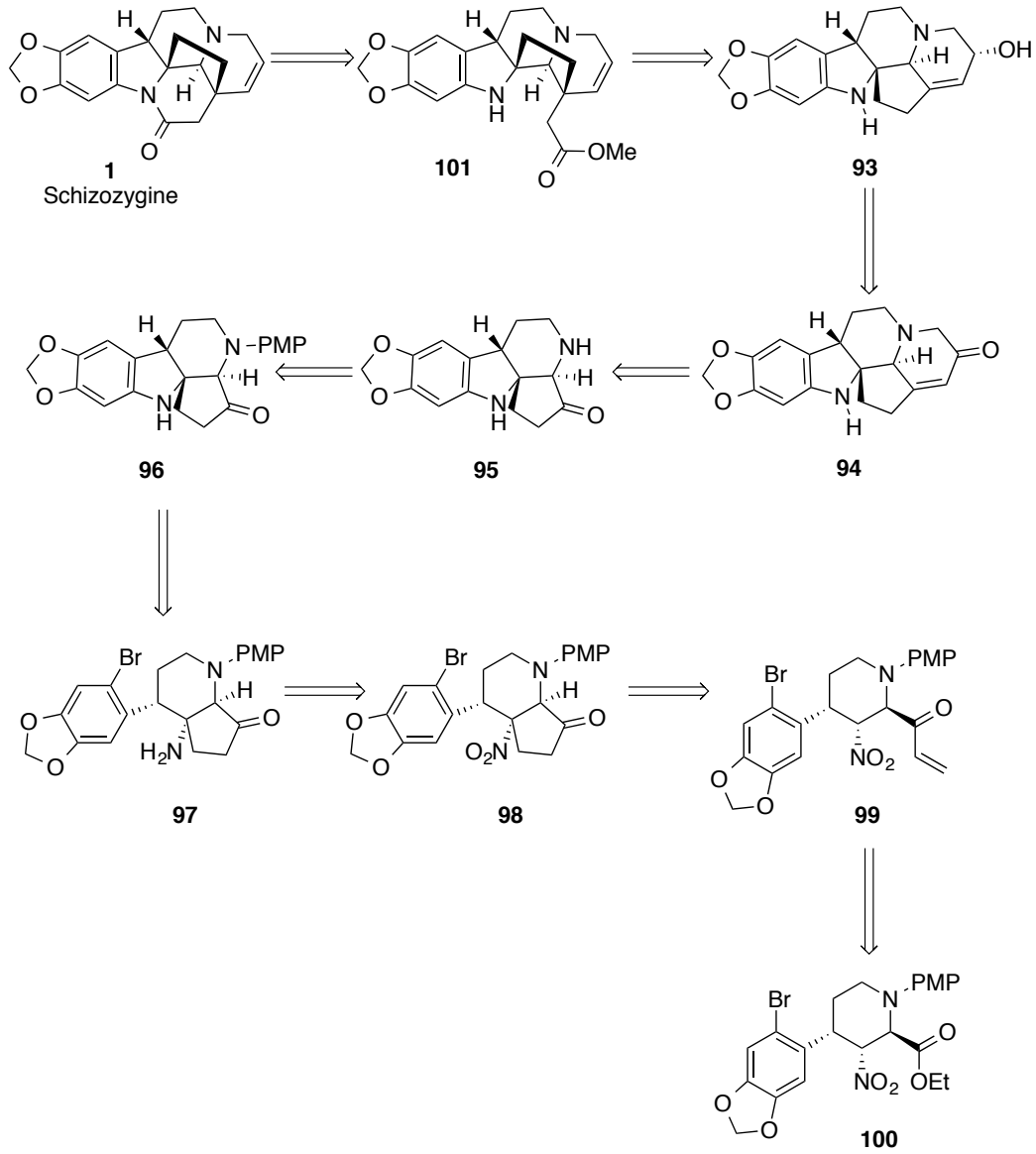
While the nitro-Mannich reaction has been extensively studied, it has only been applied to complex molecules infrequently.[14] The complex polycyclic alkaloid Schizozygine **1** is a good target to showcase nitro-Mannich chemistry as it contains a 1,2-diamine and a 2-aminomethylene indoline core (Figure 4).



1
Schizozygine

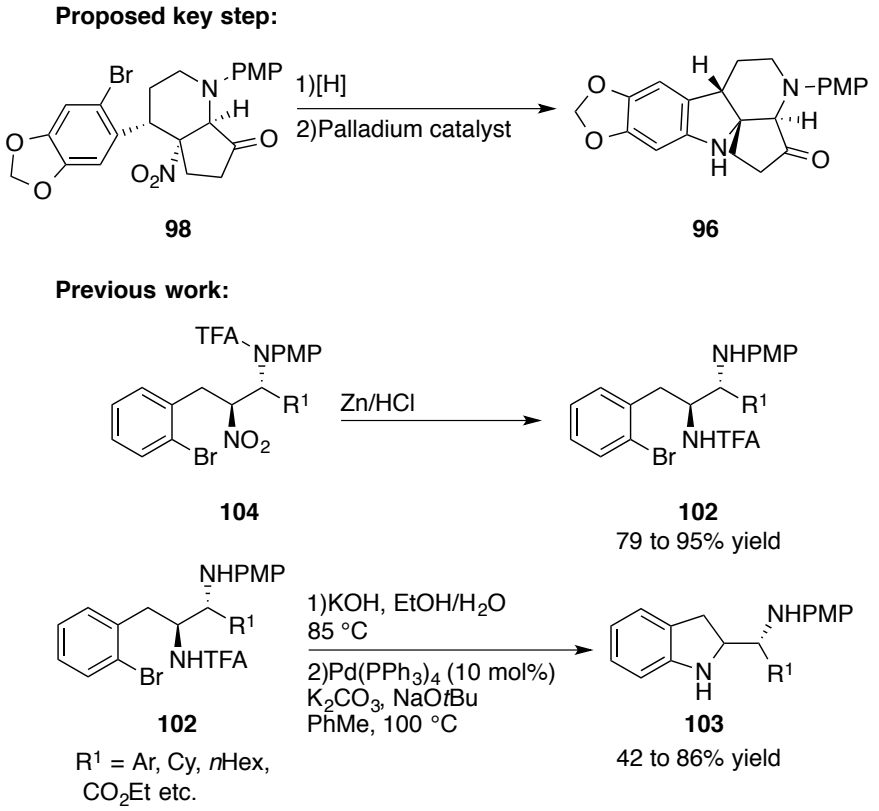
Figure 4: The alkaloid Schizozygine with the key structural elements highlighted.

A possible retrosynthesis of Schizozygine would be the following sequence (Scheme 16): Schizozygine **1** can be made from Johnson-Claisen rearrangement/lactamisation reaction from alcohol **93**, the allylic alcohol could be made by a Luche reduction of α,β-unsaturated ketone **94**. The α,β-unsaturated ketone would then be made from an aldol reaction/ring-closure sequence from **95** and **95** is made by simple PMP deprotection of **96**. A palladium catalyzed intramolecular *N*-arylation would form the tricycle **96** from amine **97** that is in turn made from reduction of nitro **98**. The bicycle **98** may form spontaneously from vinyl ketone **99** or a phosphine catalyzed Michael addition may be necessary. The vinyl ketone **99** can be made by DIBAL-H reduction of ester **100**, addition of vinylmagnesium bromide and then oxidation to the ketone.



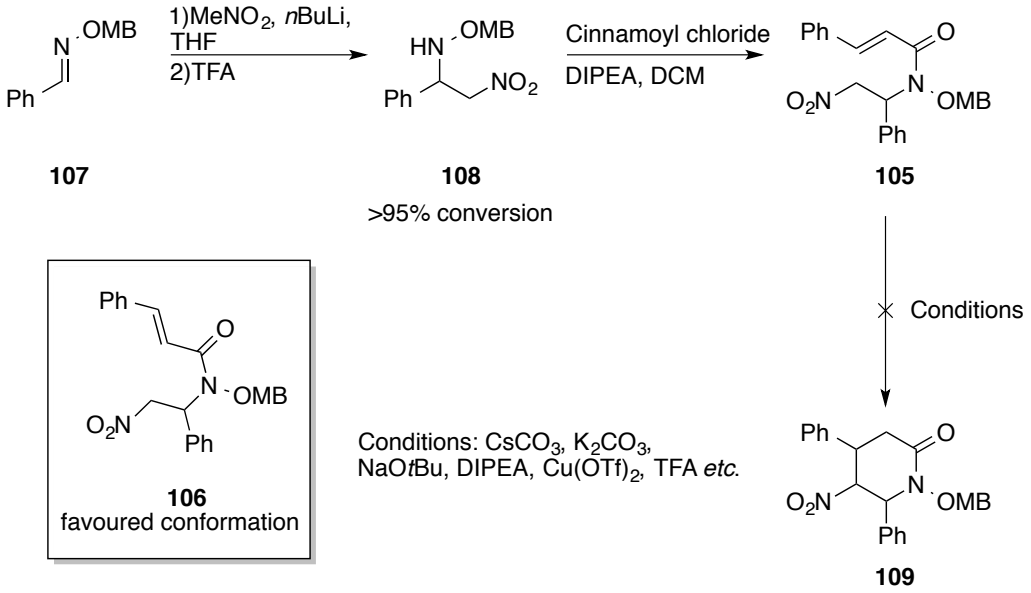
Scheme 16: Retrosynthesis of Schizozygine **1** to piperidine **100**.

A key step in this disconnection is the reduction of nitro **98** to the amine **97** and then intramolecular *N*-arylation to give tricycle **96**. This proposed transformation draws from methodology described by Anderson *et al*. that a *N*-trifluoroacetylated nitroamine can be reduced to an orthogonally protected diamine **102** and then converted to the indoline **103** using a Pd(0) catalyst (Scheme 17).[51]



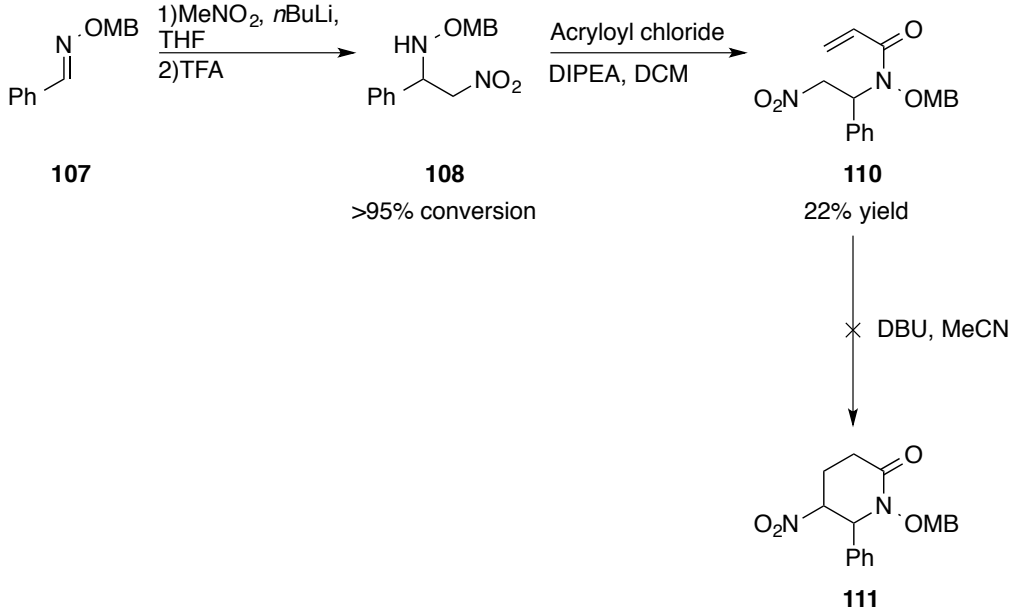
Scheme 17: Key methodology relating to the intramolecular Buchwald-Hartwig reaction.

As the piperidine core contains a 1,2-nitroamine, it was thought that the nitro-Mannich reaction could make piperidine **100** stereoselectively. The synthesis of the piperidine core was first investigated within the group by an intramolecular conjugate addition cyclisation; this was tested using model system **105** (Scheme 18). It was found that no cyclisation occurred, despite extensive investigation into different reaction conditions. It was hypothesised that this cyclisation was unsuccessful as the favoured conformation of **105** was where the double bond is distal to the nitro group **106**, preventing steric clash.[180]



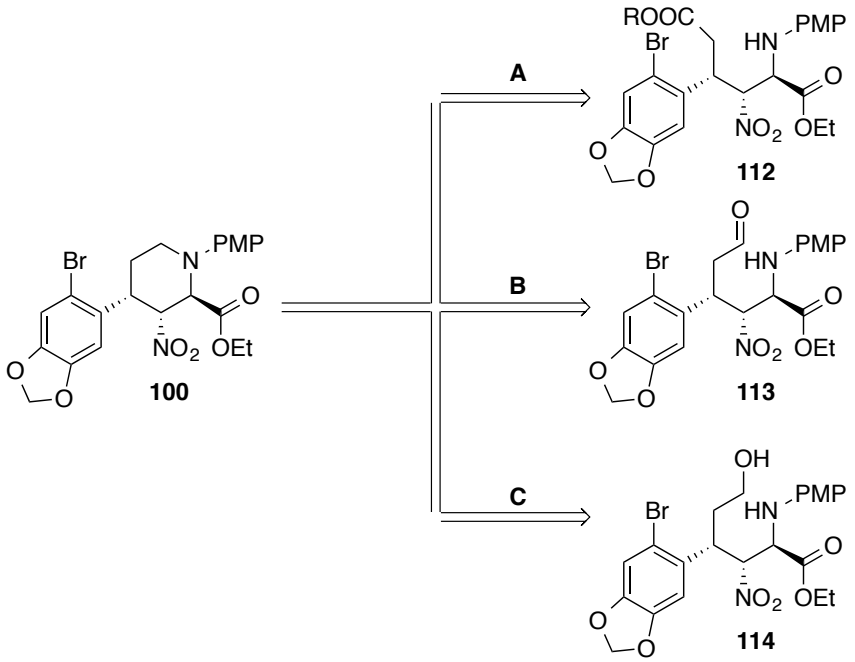
Scheme 18: Previous investigations into an intramolecular route to Schizozygine **1**.[180]

To confirm if the cyclisation was unsuccessful due to a conformational issue, the cyclisation was investigated using the *N*-acrylate **110** (Scheme 19). Unfortunately when the *N*-acrylamide was treated with DBU degradation occurred and no desired product **111** was observed.[180]



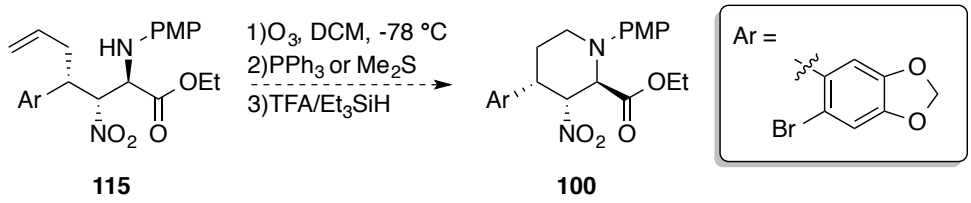
Scheme 19: Further investigations into a conjugate addition route to piperidinone **110**.[180]

As this retrosynthesis was not providing any useful results a new retrosynthesis to the key piperidine intermediate was then proposed. Piperidine **100** could then be disconnected back to three nitroamines **112**, **113** or **114** (Scheme 20). Each nitroamine shares the core structure but has a different oxidation state. Disconnection A involves a nitro-Mannich/lactamisation reaction, to give a piperidone that can be easily reduced to the piperidine **100**. Disconnection B utilizes a direct reductive amination reaction to give piperidine **100**. Disconnection C would involve an intramolecular cyclisation; a similar transformation has previously been developed within the group.[50]



Scheme 20: Possible disconnections of piperidine **112**, **113** and **114** back to structurally related 1,2-nitroamines.

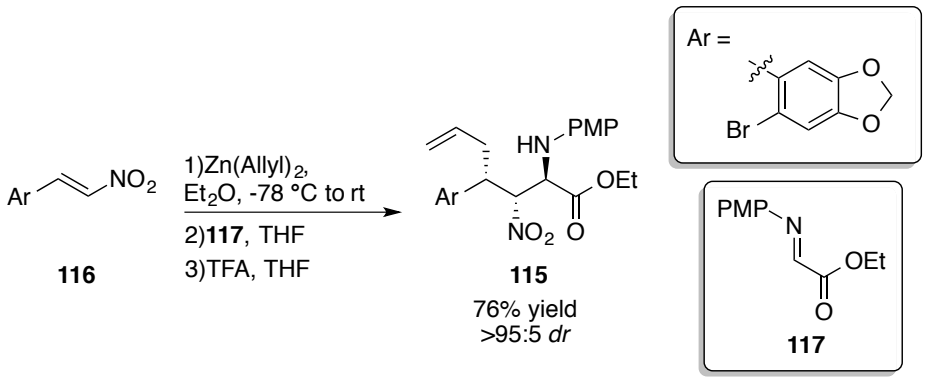
Retrosynthesis B was briefly investigated within the group by Adam Noble. It was thought that nitroamine **115** could be transformed to the piperidine by an ozonolysis/reductive amination sequence (Scheme 21).



115 **100**

Scheme 21: Reductive amination route to piperidine **100**.

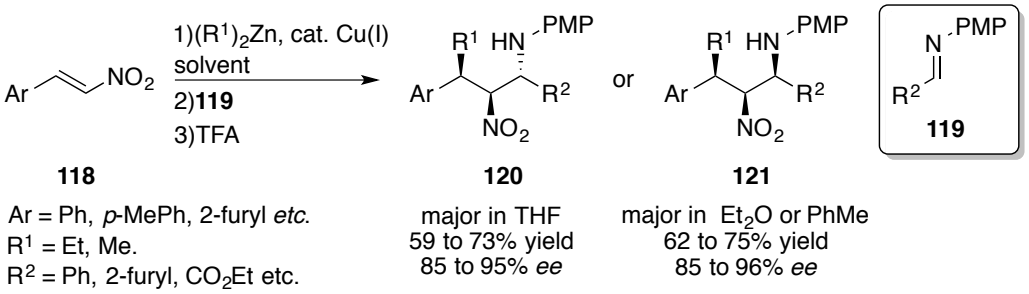
It was found that 1,2-nitroamine **115** could be made in high diastereoselectivity and yield, through a three-component coupling between diallylzinc, nitrostyrene **116** and imine **117** (Scheme 22). An enantioselective synthesis of nitroamine **115** was not investigated.[181]



116 **115** 76% yield >95:5 *dr* **117**

Scheme 22: Three-component coupling to give nitroamine **115**.

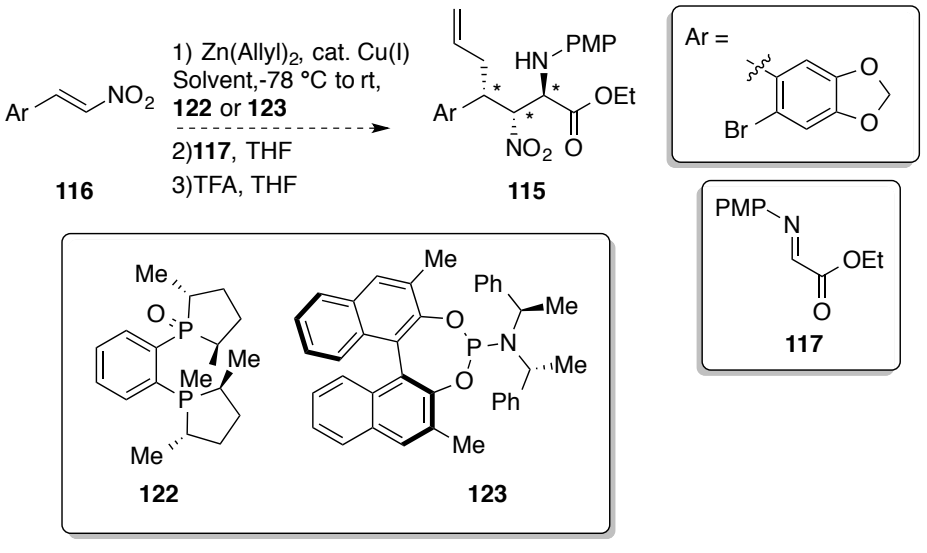
This procedure builds on work by Anderson *et al*. where it was found that a substituent on the β-position controls the stereochemical course of a nitro-Mannich reaction (Scheme 23).[44] The same study found that a solvent switch leads to different diastereomers; the stereochemical course is dictated by the solubility of the $Zn(OCOCF_3)_2$ product in different solvents.



Scheme 23: Synthesis of 1,2-nitroamines with three contiguous stereocenters.

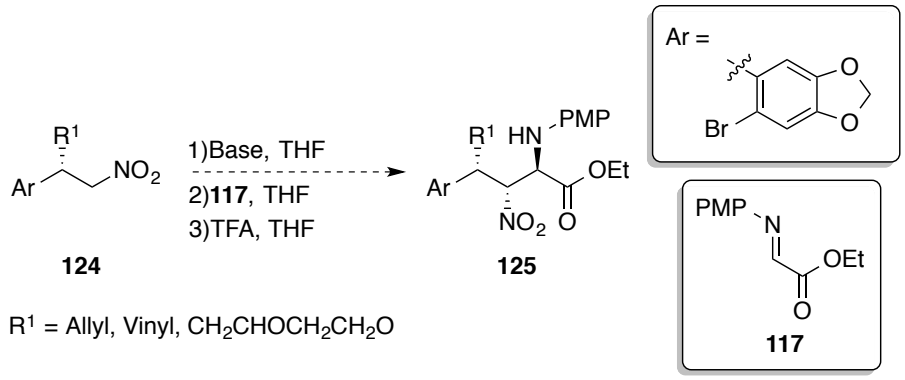
While this disconnection looks promising, there are two significant challenges: Diallylzinc is thought to be more reactive than diethylzinc, hence enantiocontrol might be difficult. Also the enantioselective conjugate addition to nitrostyrenes is frequently intolerant to *ortho*-substituents, providing an extra level of difficulty.[118]

A feasibility study into the enantioselective addition of diallylzinc using common ligands (**122** and **123**) would provide an insight into whether a three-component coupling will provide the desired enantioenriched nitroamine in high yields and diastereoselectivity (Scheme 24).



Scheme 24: Proposed enantioselective addition of reactive organozinc reagents.

Alternatively one could synthesise the nitroalkane **124** separately and then use it in a nitro-Mannich reaction. This could give the enantioenriched nitroamine **125** without the need to develop novel dialkylzinc related methodology (Scheme 25).

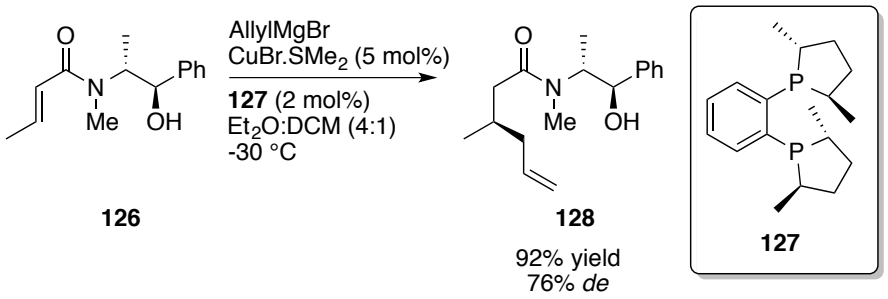


Scheme 25: Standard nitro-Mannich approach to nitroamine **125**.

3.0 Results and Discussion

3.1 Addition of Organozinc Reagents to Nitrostyrene 116

In order for an enantioselective three-component nitro-Mannich reaction to be successful, the initial enantioselective conjugate addition must occur with high conversion and *ee*. There are no instances of an enantioselective addition of diallylzinc to nitrostyrenes or other Michael acceptors and there are scarcely any reports of Grignards undergoing an enantioselective Michael addition either. The most promising report is by Woodward *et al*. who described a stereoselective 1,4-addition of allylmagnesium bromide to α,β-enamide **126** using ligand **127** in conjunction with a chiral auxiliary (Scheme 26).[182]



Scheme 26: Related stereoselective addition of allylmagnesium nucleophiles.

To investigate if this was a realistic retrosynthesis of nitroamine **115**, a study of ligands previously used within the group was performed. The ligands Bozphos **122**[44] and phosporamidite **123**,[117] have previously been successful within the group and so were used as model ligand systems for this chemistry. If there was a good degree of enantioselectivity then a detailed ligand screen could be performed, as there are a variety of ligands shown to be effective in the copper catalyzed asymmetric conjugate addition of dialkylzincs (Figure 5).

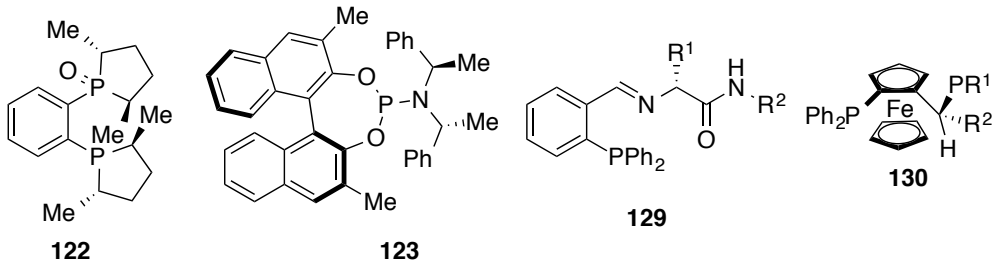
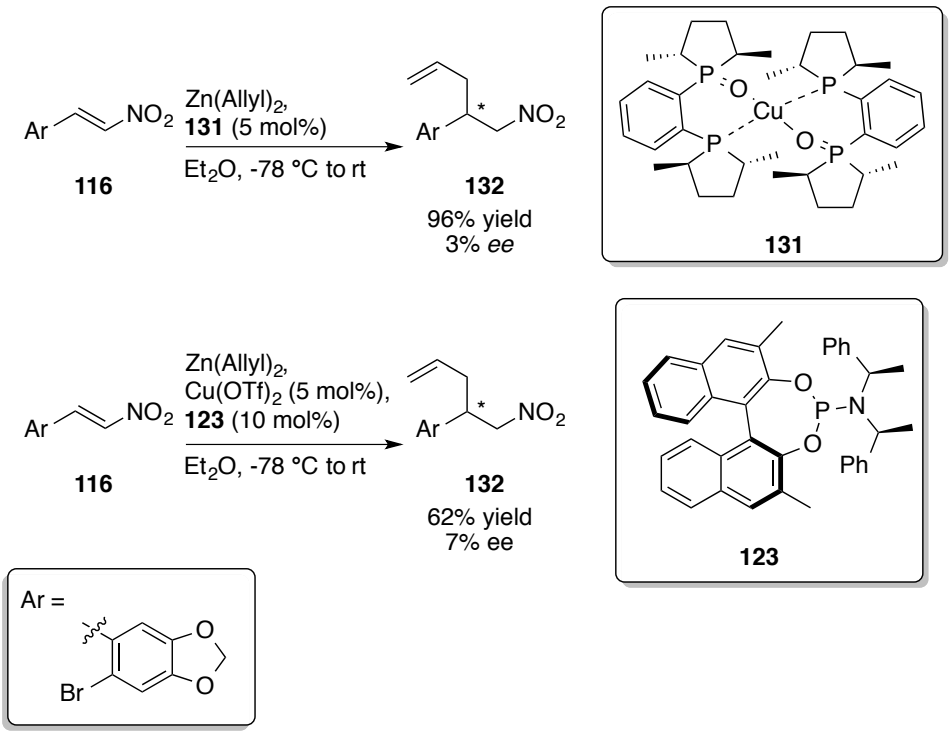


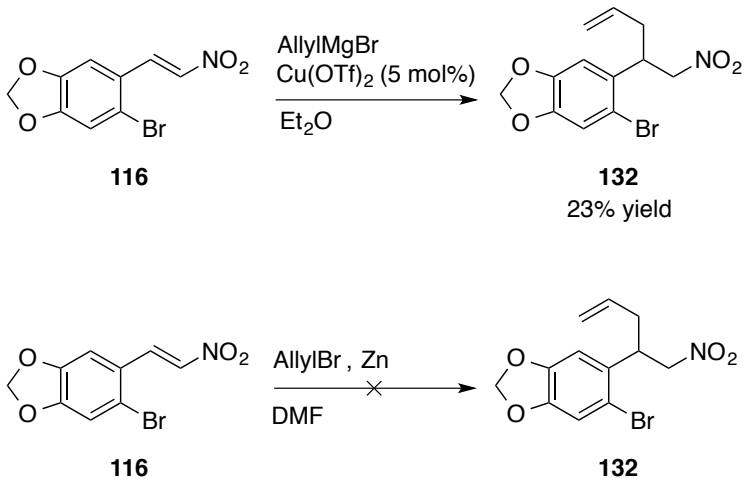
Figure 5: Ligands **122** and **123** and others that could investigated.[183]

Addition of diallylzinc[184] to nitrostyrene **116** in the presence of catalytic $Cu(OTf)_2$ and ligands **122** or **123** failed to give any meaningful stereo-induction (Scheme 27). It is thought that enantioselective addition was not possible as diallylzinc is too reactive.



Scheme 27: Investigating asymmetric addition of diallylzinc.

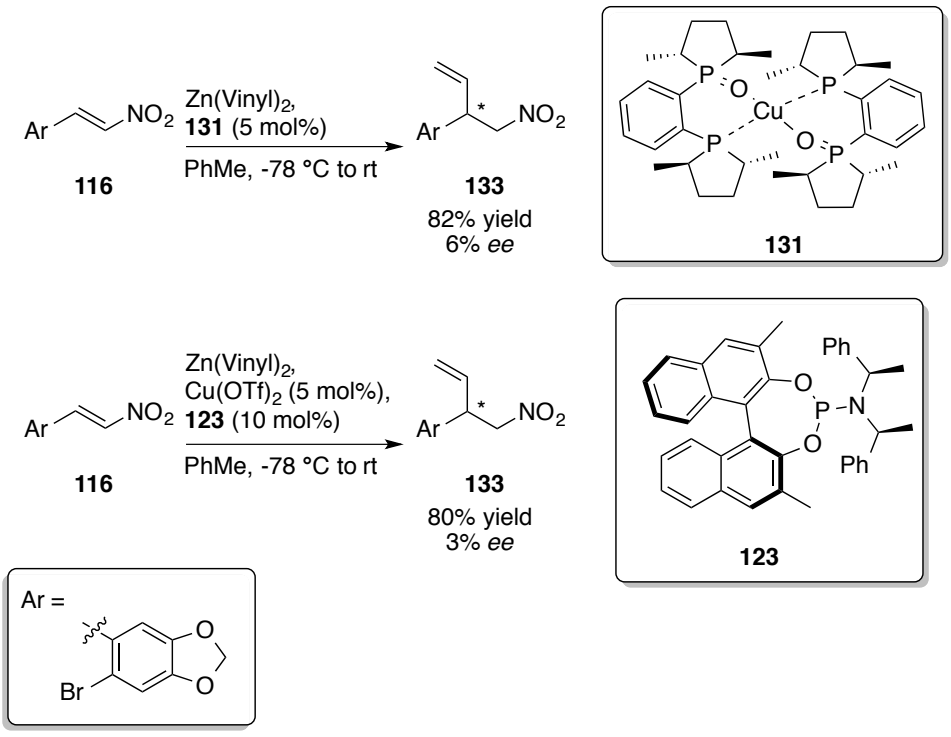
The less reactive allylzinc bromide and allylmagnesium bromide were also investigated as nucleophiles. Use of allylmagnesium bromide gave a poor yield of 23%, while allylzinc bromide (made by allyl bromide and metallic zinc) gave none of the desired product, only recovered starting material (Scheme 28). The low yield when allylmagnesium bromide was used meant that an enantioselective procedure was not investigated.



Scheme 28: Investigation into using alternative allyl nucleophiles.

Divinylzinc as a nucleophile

As a vinyl group can also be transformed to an aldehyde,[185] and divinylzinc has previously been used in enantioselective reactions,[186] addition of divinylzinc to nitrostyrene **116** was then investigated, using the same ligand/catalyst combinations. Unfortunately addition of divinyl zinc was high yielding but provided equally terrible enantioselectivites as diallylzinc (Scheme 29).

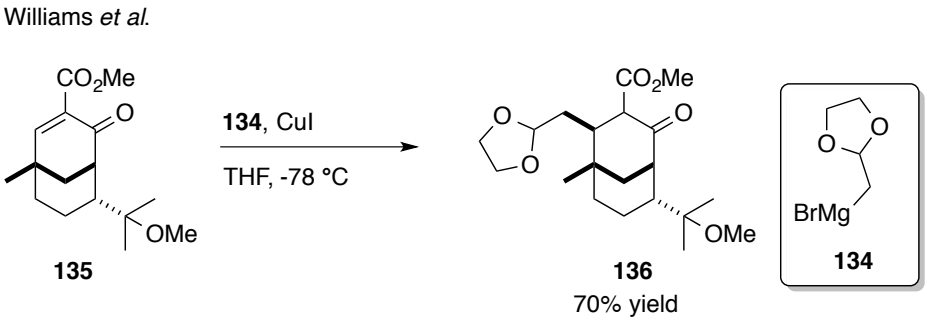


Scheme 29: Investigating asymmetric addition of divinylzinc.

It became clear that the diallyl and divinyl zinc reagents were not appropriate nucleophiles for an enantioselective reaction. Even with an extensive ligand, solvent and catalyst screen it was thought that generating an acceptable enantiomeric excess would be difficult. In light of these difficulties an alternative nucleophile was investigated.

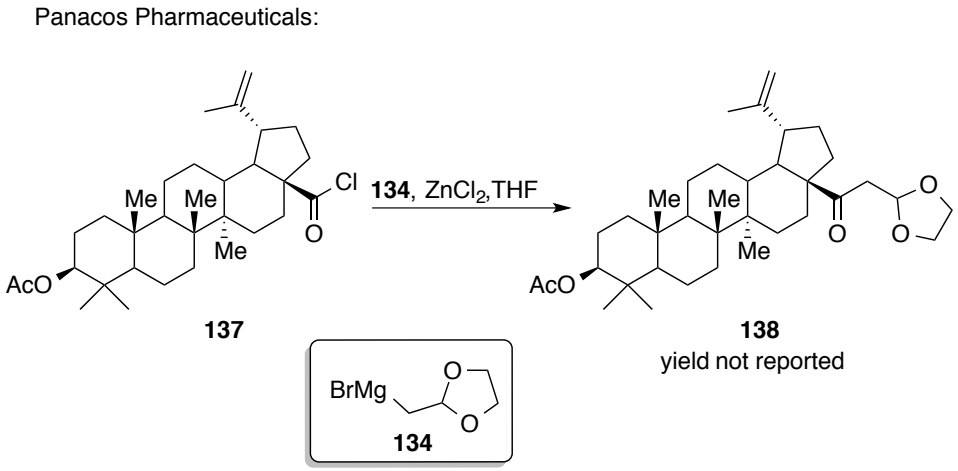
3.2 Dioxolane as a Nucleophile

There have been reports of copper catalyzed conjugate additions of dioxolane Grignard **134** to α,β-unsaturated esters (Scheme 30).[187]



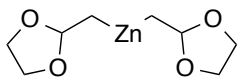
Scheme 30: Copper catalyzed addition of dioxolane Grignard.

A patent by Panacos Pharmaceuticals described the use of Grignard **134** with zinc (II) chloride as an organozinc nucleophile (Scheme 31).[188]



Scheme 31: *In situ* generation of alkylzinc reagent.

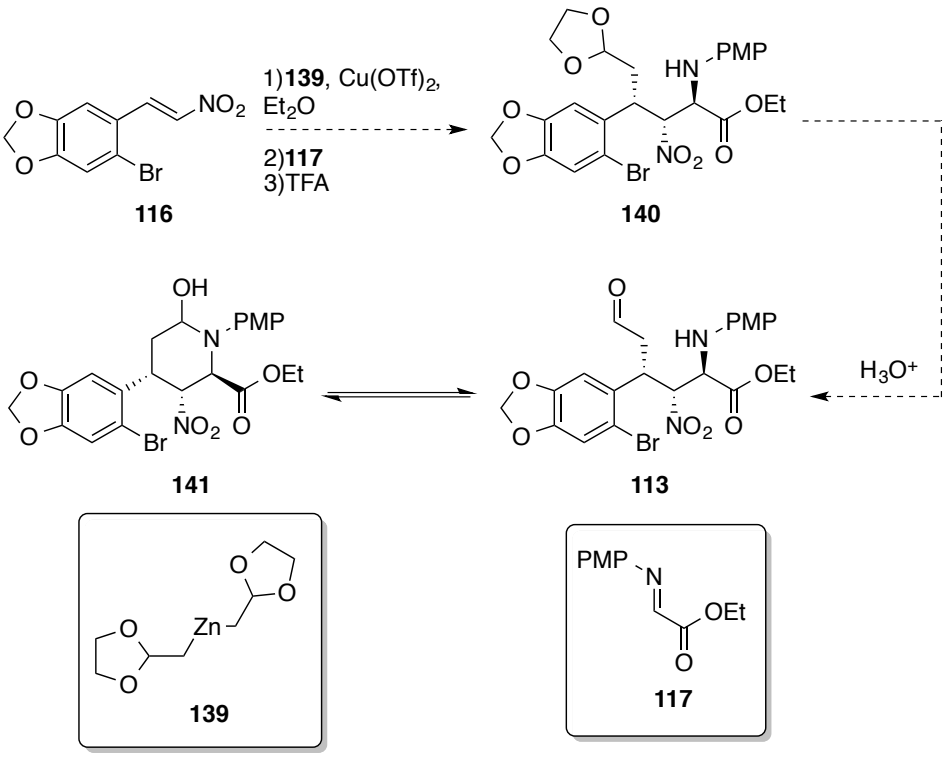
These encouraging reports indicated that dialkylzinc **139** might provide a solution to multiple synthetic problems at once. Structurally, dialkylzinc **139** is close to diethylzinc and therefore may react in a similar manner and may be amenable to enantiocontrol using chiral ligands (Figure 6).



139

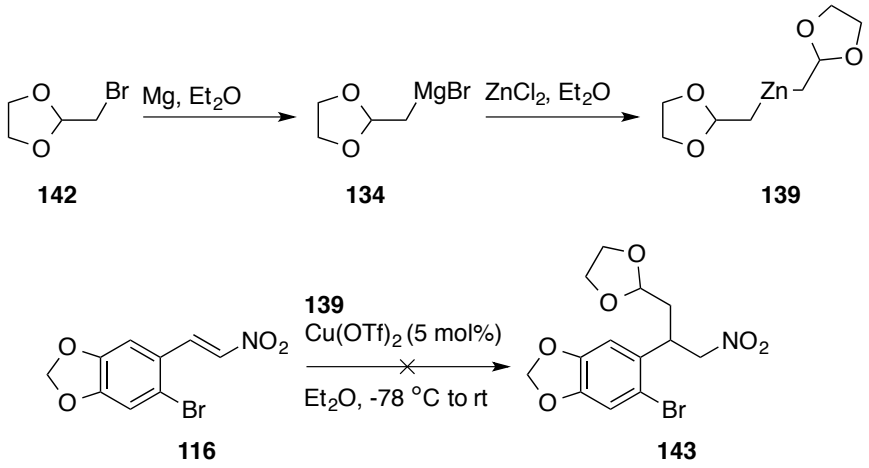
Figure 6: Proposed organozinc nucleophile.

The dialkylzinc **139** could be generated *in situ* from the commercially available Grignard **134**, and then may undergo an enantioselective conjugate addition reaction to nitrostyrene **116**. If this was possible, the three component nitro-Mannich reaction could be performed. Acidic deprotection of nitroamine **140** would give the desired aldehyde **113**/hemiaminal **141** (Scheme 32). This synthetic sequence would remove the redox steps that were necessary when following the diallylzinc disconnection.



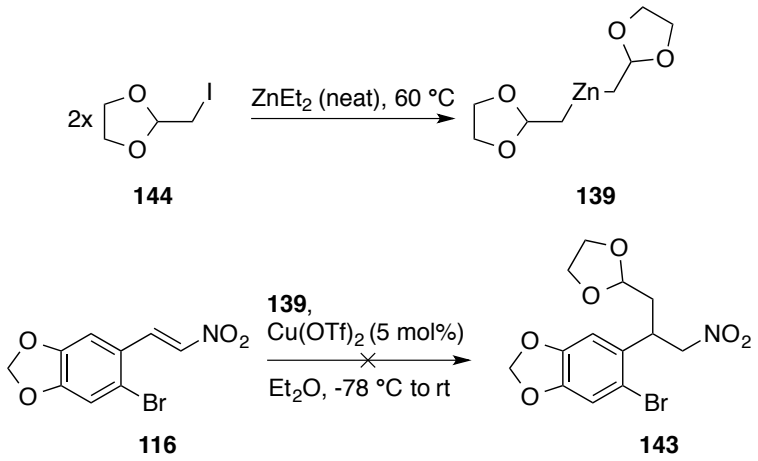
Scheme 32: Use of dialkylzinc **139** for the expedient synthesis of nitroamine **140**.

Addition of dialkylzinc reagent **139** (generated by metathesis with $ZnCl_2$) to nitrostyrene **116** and $Cu(OTf)_2$ led to no reaction over a period of days. This disappointing result led us to believe that the commercially available Grignard had decomposed prior to use. When the bottle was titrated using the method described by Knochel *et al*.[189] there appeared to be no Grignard reagent. The Grignard was then made fresh from the corresponding alkyl bromide and then the dialkylzinc made *in situ* from the Grignard. This also gave no reaction but a bright green turbid solution formed upon addition of the dialkylzinc **139** to the reaction mixture (Scheme 33).



Scheme 33: Repeated addition of dialkylzinc **139**.

The neat dialky zinc was then made by a metathesis reaction using diethylzinc and alkyliodide **144** as described by Knochel *et al*.[190] to make sure the dialkylzinc was being made. When the dialkylzinc reagent was added to the reaction mixture the solution turned bright green and turbid once again (Scheme 34).



Scheme 34: Generation of neat dialkylzinc **139** and its use in the copper catalyzed conjugate addition reaction.

It is thought that the bright green colour might be from a newly formed copper complex being made. The copper complex could then form oligomers.[191] Previous literature has shown that having coordinating groups on an organocopper reagent can lead to decreased reactivity or render them insoluble. Wittig *et al*. synthesised a similar α-oxygenated dialkylzinc reagent **145** and this was found to form a stable chelate that could be isolated (Figure 7).[192] It is feasible to infer that dialkylzinc **139** may form a stable chelate and so would the cuprate.

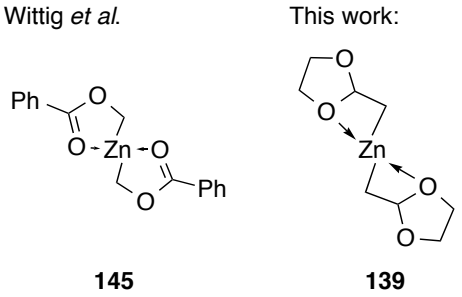
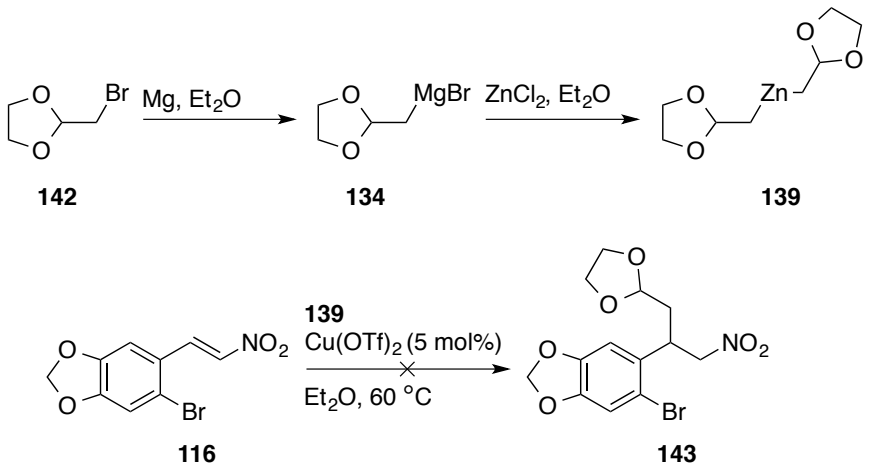


Figure 7: Chelate observed by Wittig *et al* and its similarity to dialkylzinc **145**.

In an attempt to break up the oligomers, without using additives such as HMPA, the reaction mixture was heated to 60 °C for 24 h; this still led to no consumption of the starting material (Scheme 35).

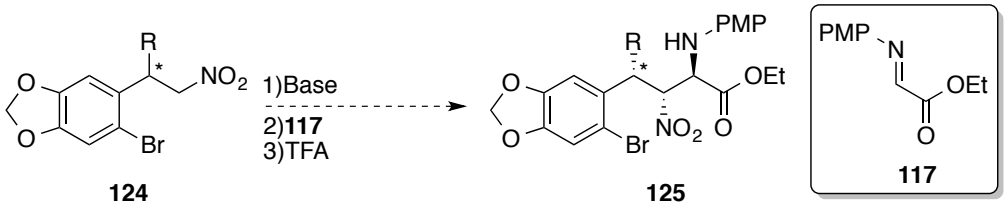


Scheme 35: Attempted thermal deaggregation of dialkylzinc **139**.

With such poor results using dialkylzinc nucleophiles, it became apparent that a three-component coupling was not going to be the best route to nitroamine **140**. Most dialkylzinc methodology only uses diethylzinc and dimethylzinc as nucleophiles in their substrate scope. This work has highlighted that while the enantioselective conjugate addition of dialkylzinc reagents does occur with high yields and enantioselectivities, work is needed to extend the conditions to less mundane nucleophiles. The lack of success using dialkylzinc chemistry could also be attributed to nitrostyrene **116** having an *ortho*-halide; *ortho* substituted nitrostyrenes have been noted as difficult substrates.[52]

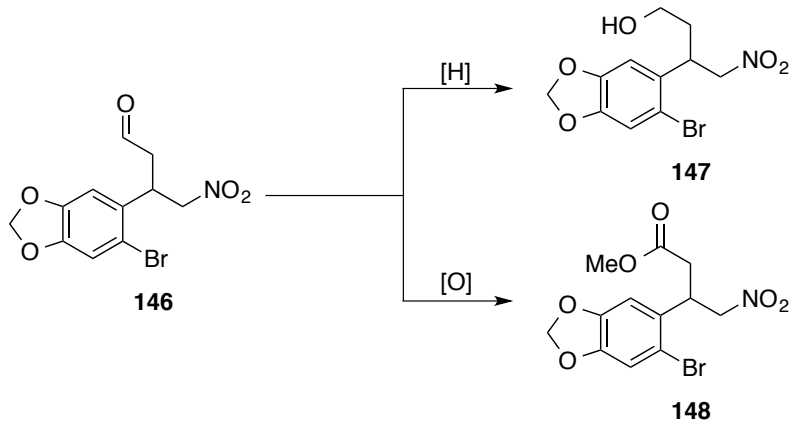
3.3 Organocatalytic Route to *syn*,*anti* Nitroamines

A different strategy was investigated: synthesis of an enantioenriched β-functionalised nitroalkane and then use of this in the nitro-Mannich reaction. The group on the β-position should still control the relative stereochemistry of the nitroamine product (Scheme 36).[44]



Scheme 36: Revised approach to *syn*,*anti*-nitroamine **125**.

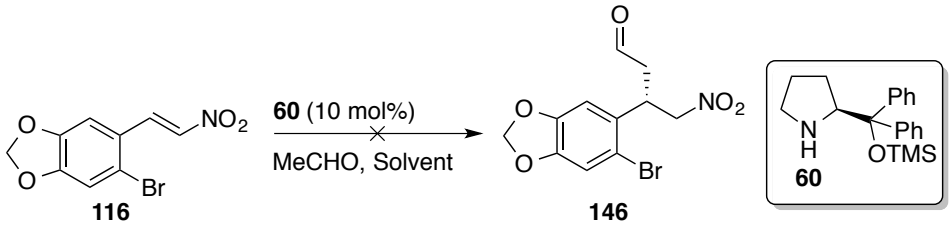
Following our previous disconnections, R groups with a similar size to an alkyl group could be on the β-position and control the stereochemical course of the nitro-Mannich reaction. The most reasonable R groups could be $–CH_2CO_2Et$, $-CH_2CHO$ or $-CH_2CH_2OH$, with the aldehyde or alcohol protected. A literature review found that all three nitroalkanes were made by the same sequence, direct synthesis of the aldehyde and then either reduction or oxidation to give the alcohol or ester (Scheme 37).



Scheme 37: Approach to enantioenriched nitroalkanes **147** and **148**.

3.4 Synthesis of Aldehyde 146

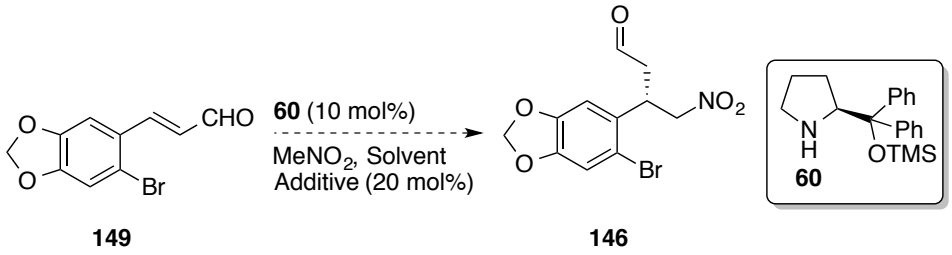
To make aldehyde **146** an organocatalytic addition of acetaldehyde to nitrostyrene **116** was attempted. Hayashi *et al*.[193] and List *et al*.[194] have previously reported that using TMS-prolinol **60** with acetaldehyde gives similar nitroalkanes in high yields and enantioselectivity. When the reaction was repeated with nitrostyrene **116** there was no reaction (Scheme 38). During these reactions nitrostyrene **116** was not soluble, or sparingly soluble, this could be the main reason why the reaction did not proceed. A solvent screen failed to improve the situation, even when the nitrostyrene was soluble in the reaction solvent (DCM).



Solvents: MeCN, Dioxane, DCM, PhMe

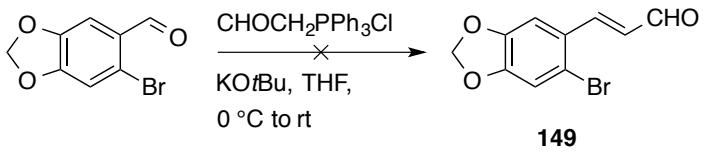
Scheme 38: Attempted organocatalytic addition of acetaldehyde to nitrostyrene **116**.

As there seemed to be no promising solvents to allow this reaction to proceed, a different tactic was used. Instead of attacking a nitrostyrene with acetaldehyde, the same product could be made by organocatalytic addition of nitromethane to an α,β-unsaturated aldehyde **149** (Scheme 39).



Scheme 39: Proposed alternative synthesis of aldehyde **146**.

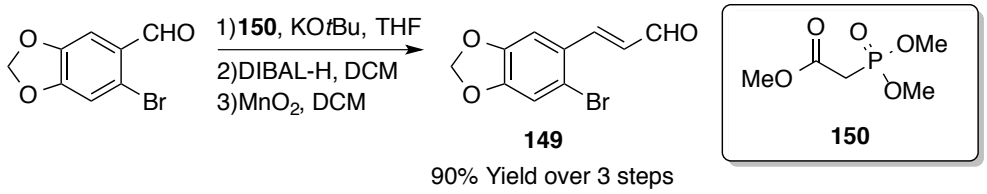
Synthesis of the α,β-unsaturated aldehyde starting material **149** was attempted by a direct Wittig reaction between 6-bromopiperonal and formyltriphenylphosphonium chloride in the presence of KO*t*Bu, but this was unsuccessful (Scheme 40).



Scheme 40: Attempted Wittig reaction to give aldehyde **149**.

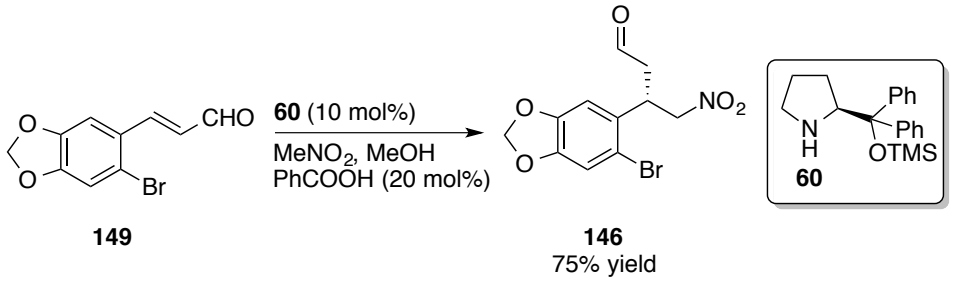
The synthesis of the aldehyde starting material **149** was achieved in 3 steps from 6-bromopiperonal, in a yield of 90% (Scheme 41). This was done by a Horner-Wadsworth-Emmons reaction to give the α,β-

unsaturated ester, reduction to the allylic alcohol with DIBAL-H and then oxidation to the aldehyde using MnO_2. A benefit of this procedure was it could be scaled to multi-decagram quantities with little change in yield and could be purified by recrystallisation, with no column chromatography necessary.



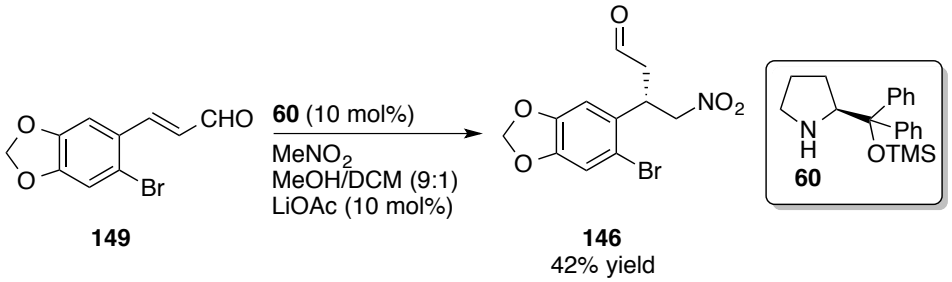
Scheme 41: Synthesis of aldehyde **149**.

With a robust method of making the key aldehyde **149** at hand, our attention turned to the synthesis of aldehyde **146**. Hayashi *et al*.[195] and Jørgensen *et al*.[196] have demonstrated the addition of nitromethane to arylacrylates using TMS-Prolinol catalyst **60;** this happens in good yields and enantioselectivity. Using the procedure developed by Jørgensen *et al*. gave the desired alkyl aldehyde **146** in a yield of 75% (Scheme 42).



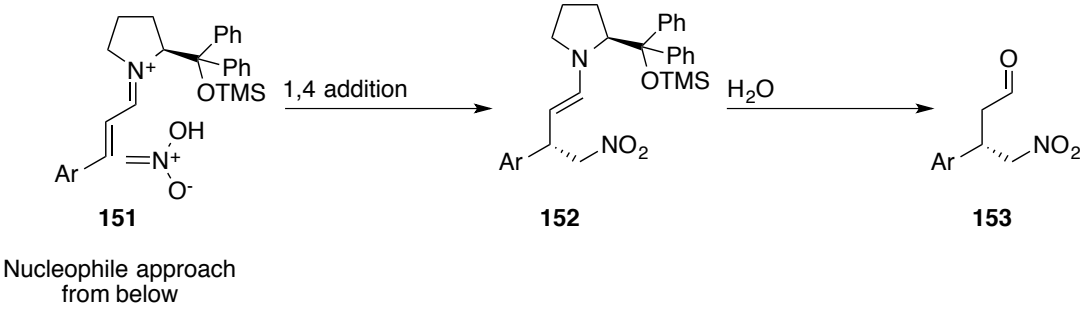
Scheme 42: Synthesis of aldehyde **146**.

An improved procedure reported by Ye *et al*. where benzoic acid was replaced with lithium acetate gave a lower yield of 42% (Scheme 43).[197]



Scheme 43: Attempted improvement of the asymmetric conjugate addition of nitromethane.

The absolute stereochemistry was assigned by comparison of the optical rotations reported by Jørgenson *et al*. and Hayashi *et al*. Typically the product formed by a prolinol **60** catalyzed Michael addition can be easily predicted by placing the incoming nucleophile at the opposite face to the sterically demanding group on the heterocycle (Scheme 44). This work appears to follow the same predicted stereochemical outcome.



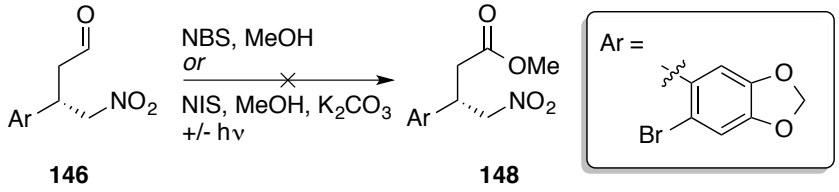
Scheme 44: Proposed prolinol catalyzed addition of nitromethane mechanism.

The *ee* of the reaction is typically measured indirectly by conversion of the aldehyde to the acetal, alcohol or carboxylic acid. The same process was applied to **146**.

3.5 Investigations Using Ester 148

Attempts to convert aldehyde **146** to the ester **148** using an oxidative esterification procedure as described by Jørgenson *et al*. were unsuccessful.[196] This procedure only gave a complex mixture when analyzed by ^{1}H NMR. Replacement of the oxidant from NBS to

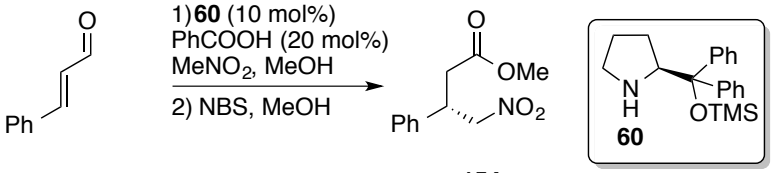
NIS/K_2CO_3 or performing the reaction in the dark also gave a complex mixture (Scheme 45).[198]



146 **148**

Scheme 45: Attempted oxidative esterification

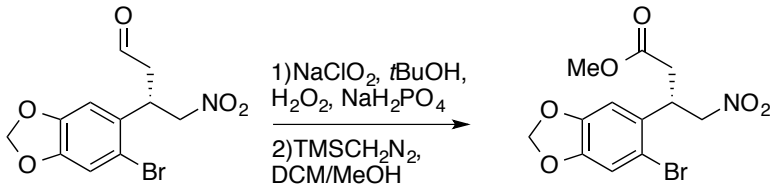
The literature procedure was then repeated using cinnamaldehyde as the starting material; this gave the ester in a similar yield as the literature (Scheme 46).[196] With this result in mind, the lack of conversion is thought to be due to the substrate, not the procedure.



154
90% yield

Scheme 46: Repetition of the literature procedure.

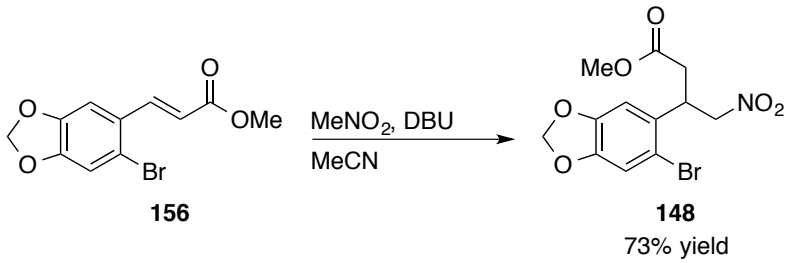
As an oxidative esterification procedure was not successful, aldehyde **146** was converted to the carboxylic acid **155** by a Pinnick oxidation. The crude carboxylic acid **155** was then methylated using TMS-diazomethane to give the desired ester **148** in 90% yield over 2 steps (Scheme 47). Analysis of the ester by chiral HPLC showed an *ee* of 97% (OD column).



146 **148**
90% yield over 2 steps
97% *ee*

Scheme 47: Synthesis of ester **148** *via* the isolated aldehyde **146**.

The racemic ester for HPLC analysis was made by addition of nitromethane to α,β-unsaturated ester **156**, with DBU as a base (Scheme 48).

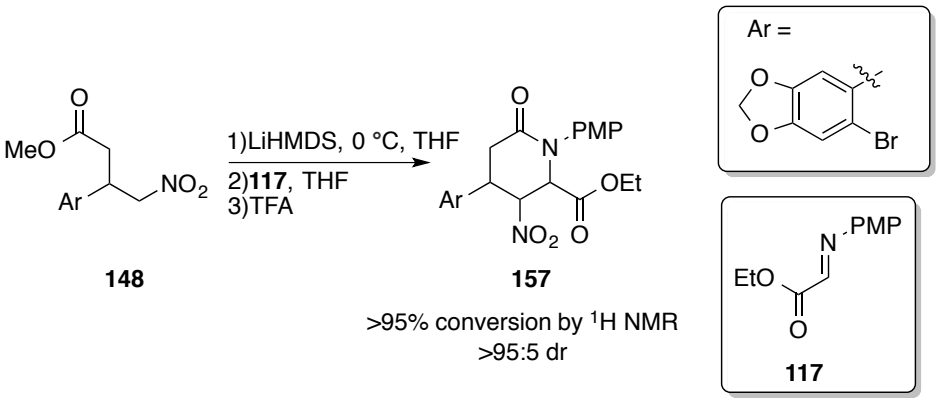


156 **148**

73% yield

Scheme 48: Synthesis of racemic ester **148**.

The ester **148** was then investigated in the nitro-Mannich reaction using LiHMDS as a base and imine **117** (Scheme 49). It appeared from the crude ^{1}H NMR that complete conversion to a new product occurred, tentatively assigned as piperidone **157**, but the product could not be separated from the excess imine. As piperidone **157** could not be isolated pure the relative stereochemistry was not determined.



148 **157** **117**

>95% conversion by ^{1}H NMR

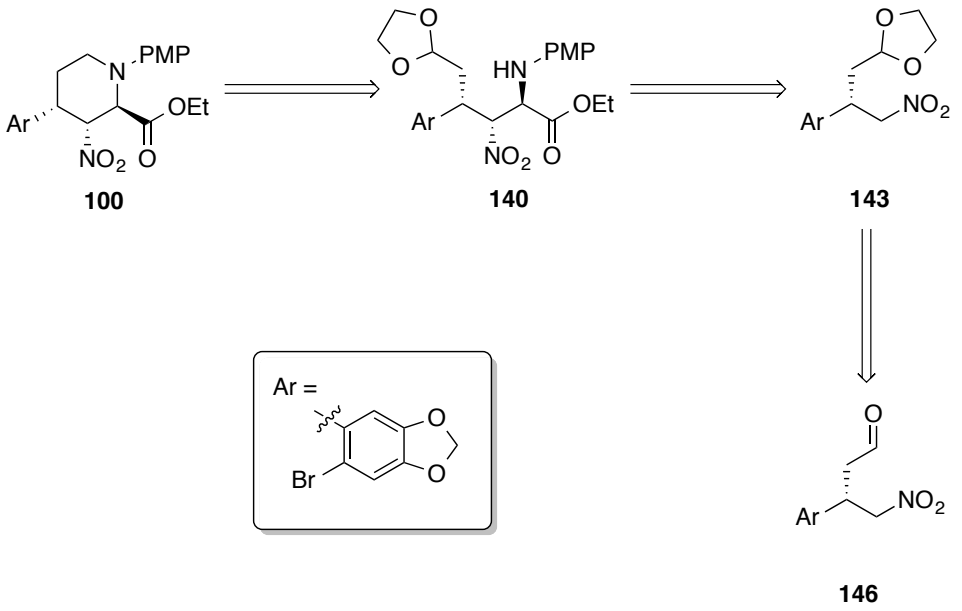
>95:5 dr

Scheme 49: Use of ester **148** in the nitro-Mannich reaction.

Further work was halted as other retrosyntheses appeared to be promising, without the need to use the highly toxic reagent TMS-diazomethane.

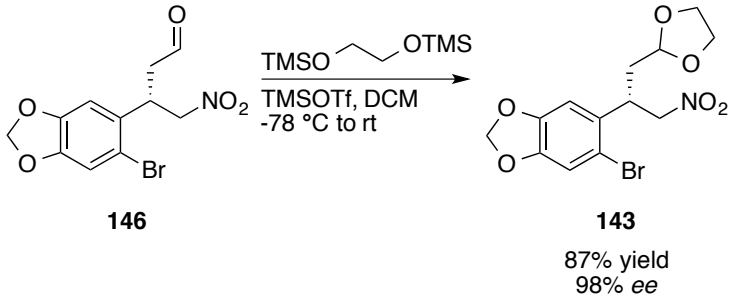
3.6 Investigations using Aldehyde 146

Another retrosynthesis that could furnish the desired piperidine **100** is by the following sequence; protection of aldehyde **146** to acetal **143**, a nitro-Mannich reaction to give nitroamine **140** and then a deprotection/reductive amination sequence to give piperidine **100** (Scheme 50).



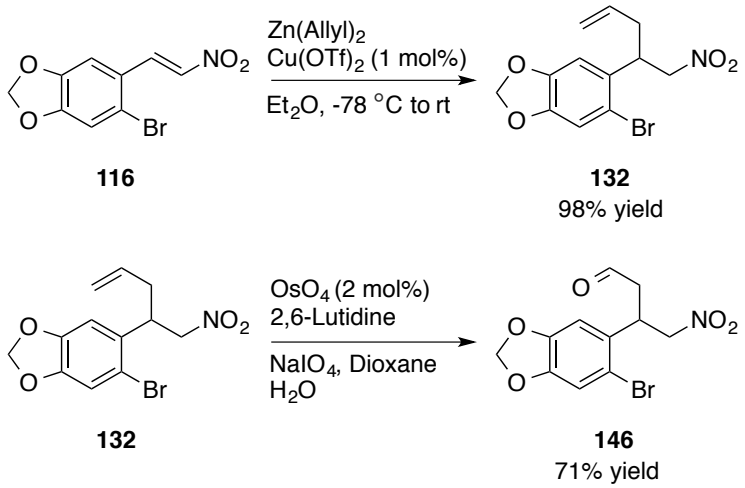
Scheme 50: Formation of piperidine **100** using aldehyde **146** as the synthon.

Protection of aldehyde **146** using TMSOTf and 1,2-bistrimethylsiloxyethane proceeded smoothly to give the dioxolane **143** in a good yield of 87% (Scheme 51). Analysis of the acetal by chiral HPLC showed an *ee* of 98%.



Scheme 51: Protection of aldehyde **146** as the acetal **143**.

In an effort to investigate the nitro-Mannich reaction quickly and at low cost, aldehyde **146** was made racemically using nitroalkane **132**. Using the diallylzinc chemistry discussed previously in this thesis, nitroalkane **132** could be made in a high yield and then converted to aldehyde **146** by a modified Lemieux-Johnson procedure (Scheme 52).[199]



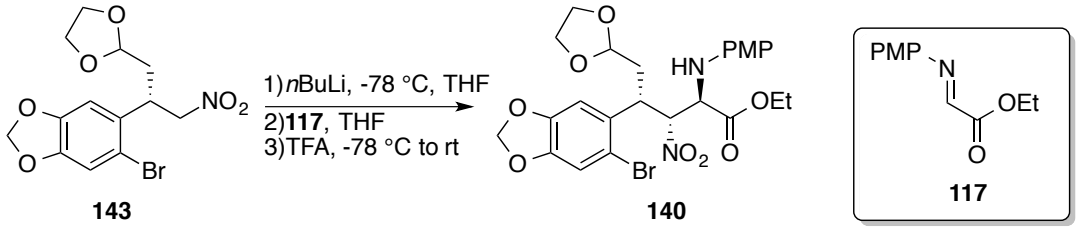
Scheme 52: Synthesis of racemic aldehyde **146**.

The aldehyde could then be protected to the dioxolane as previously described (Scheme 51). This method was used to make the racemic dioxolane reference needed for chiral HPLC analysis.

3.7 Nitro-Mannich Reaction

The nitro-Mannich reaction between protected nitroalkane **143** and imine **117** was then investigated. Non-nucleophilic bases were used to deprotonate nitroalkane **143**. In all cases no nitroamine **140** was observed, only recovered starting material (Table 1). Interestingly when *n*BuLi was used, the product was formed, albeit slowly, with only trace halogen-lithium exchange product observed in the ^{1}H crude NMR and with a *dr* of 90:5:5.

Table 1: nitro-Mannich reaction using nitroalkane **143**.



143 **140** **117**

95% conversion by ^{1}H NMR
90:5:5 dr

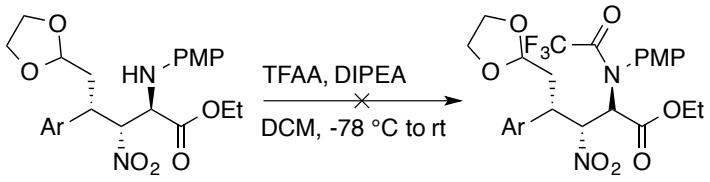
Base	Conditions (for deprotonation step)	Product[a]
LDA	1 h (-78 °C), 1 h (rt)	RSM
LiHMDS	1 h (-78 °C), 1 h (rt)	RSM
$LiNEt_2$	1 h (-78 °C), 1 h (rt)	RSM
KO*t*Bu	1 h (-78 °C), 1 h (rt)	RSM
LiH	1 h (-78 °C), 1 h (rt)	RSM
KH	1 h (-78 °C), 1 h (rt)	RSM
*n*BuLi	30 min (-78 °C)	~30% conv.
*n*BuLi	3.5 hr (-78 °C)	~95% conv.

[a]Determined by ^{1}H NMR of the crude material.

This surprising difficulty in deprotonation is attributed to the sterically congested nature of nitroalkane **143**. Some of the peaks on the ^{1}H NMR spectrum of nitroalkane **143** are very broad, indicating restricted rotation and a degree of steric encumbrance, giving some support that the area might be very sterically congested to incoming bases. Another explanation is that the nitronate intermediate is sterically hindered and addition to the iminium is slow.

It was found that the 1,2-nitroamine **140** was unstable to column chromatography, like most nitroamines. As *N*-trifluoroacetamides are stable to column chromatography a pure sample could be obtained and might be crystalline for X-ray analysis. Unfortunately there was no conversion to the trifluoroacetamide **158** (Scheme 53) and all that was recovered was starting material (with an eroded *dr*). It is thought that the nitroamine may be too sterically congested and so *N*-trifluoroacetylation

does not occur. It has also been noted by Anderson *et al*. that *syn*,*syn* nitroamines do not readily undergo trifluoroacetylation.[52]



140 **158**

Scheme 53: Attempted synthesis of the trifluoroacetamide for confirmation of the relative and absolute stereochemistry.

As an X-ray crystal structure was not obtainable, the relative stereochemistry was determined by analogy with previous work by Anderson *et al*.[44] The relative stereochemistry was assigned by comparison of the C*H*NO_2 signals and coupling constants with previously synthesised nitroamines that have been confirmed by X-ray crystallography. The nitroamine **140$_{major}$** has a C*H*NO_2 peak at 5.35 ppm and coupling constants of 10.3 and 4.5 Hz. This is consistent with previously synthesised *syn*,*anti* nitroamines; their C*H*NO_2 peaks are at 5.23 to 5.66 ppm with coupling constants of 10.5 to 10.2 Hz and 5.4 to 4.9 Hz and so nitroamine **140$_{major}$** is also assigned as the *syn*,*anti* diastereomer (Figure 7). Following from this analogy one minor diastereomer is tentatively assigned as the *syn*,*syn* diastereomer as the C*H*NO_2 peaks appear consistent with literature values. There are very limited reports of *anti*,*anti* nitroamines, and the common other minor product is the *anti*,*syn* diastereomer,[42] therefore the other minor product is assigned as the *anti*,*syn* diastereomer .[44]

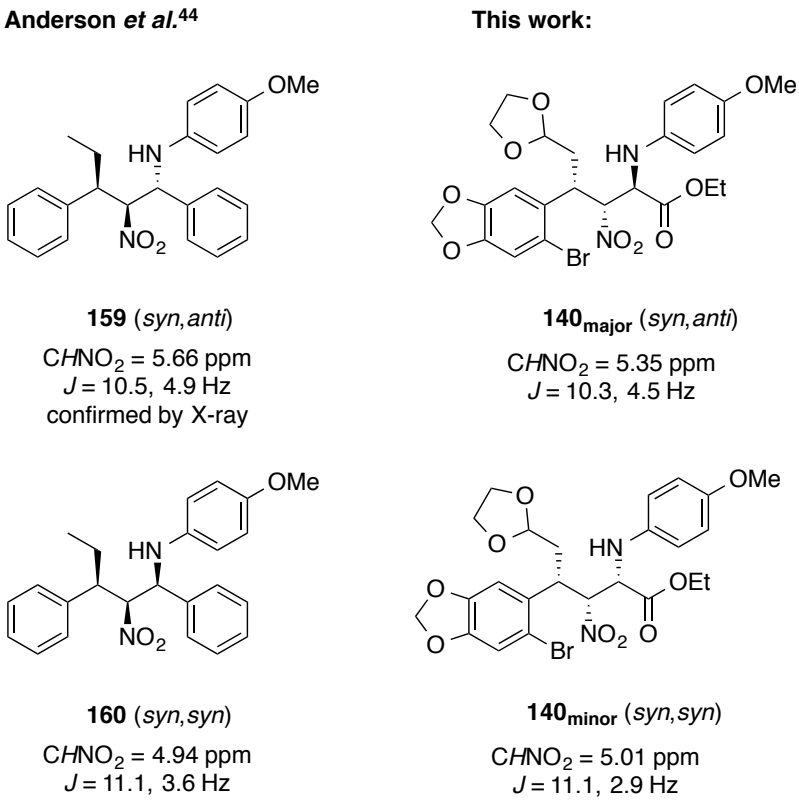
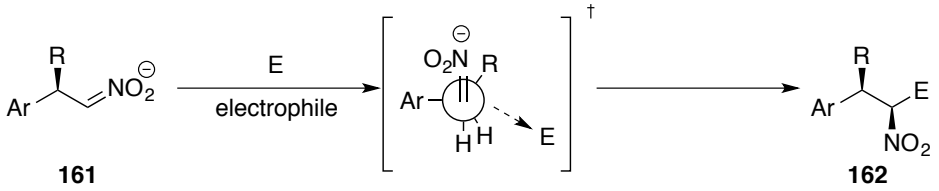


Figure 7: Assignment nitroamine **140** stereochemistry by comparison with previously assigned nitroamine **159**.

The sense of the diastereoselection can be explained by the same transition state proposed by Anderson *et al*. in their three component synthesis of *syn*,*anti* nitroamines. The *syn* relationship between the R group and the nitro group can be accounted for by a Felkin-Anh like transition state, where the α-stereocenter dictates the approach of the incoming electrophile (Scheme 54).[44]



Scheme 54: Proposed transition state to account for the high diastereoselection.

The *anti* stereoselectivity of the nitroamine is similar to previous nitro-Mannich reactions; these are thought to proceed *via* a Zimmerman-Traxler transition state (Figure 8).

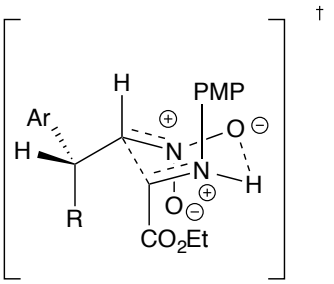
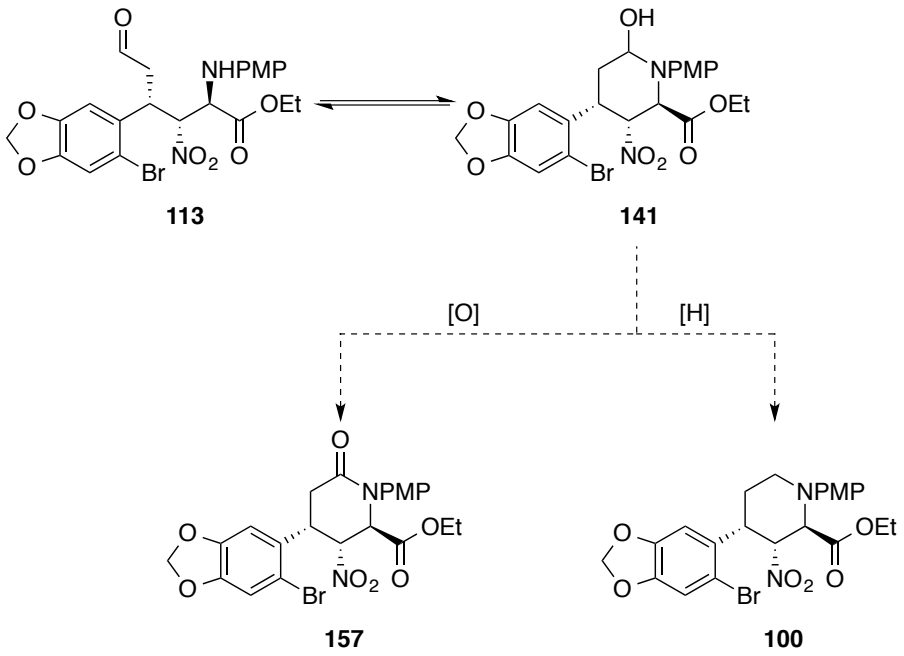


Figure 8: Origin of the diastereoselectivity.

3.8 Deprotection and Reductive Amination

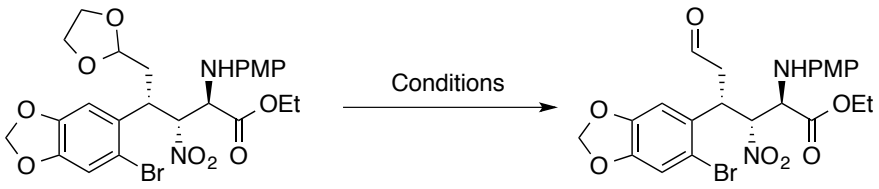
With nitroamine **140** at hand, deprotection of the acetal would give the hemiaminal **141**. The hemi-aminal could then be reduced to the desired piperidine alternatively it could be oxidized to the lactam and then reduced later in the synthesis (Scheme 55).



Scheme 55: Synthetic transformations involving hemiaminal **141**.

Standard deprotection methods were investigated; as the nitroamine functionality is prone to a retro reaction, only mild procedures were used. A selection of different procedures failed to deprotect the dioxolane moiety to the aldehyde; either the starting material was recovered (with an eroded *dr*) or complete decomposition occurred (Table 2).

Table 2: Investigation into acetal deprotection.



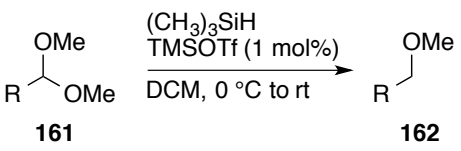
140 **113**

Reagent	Conditions	Product[a]
PPTS	Acetone (wet), rt	RSM
I_2	Acetone (wet), rt	RSM
AcOH	rt	RSM
AcOH	Reflux	Decomp.
1.0M HCl	Acetone (wet), rt	RSM
Ph_3BF_4	DCM, 0 °C	Decomp.

[a]Conversion determined by ^{1}H NMR of crude material and by TLC.

With a lack of success using standard deprotection methods, a reductive intramolecular cyclisation of nitroamine **140** to piperidine **100** was attempted, drawing inspiration from methodologies reported by Noyori *et al*.[200] and Rayner *et al*. (Scheme 56).[201]

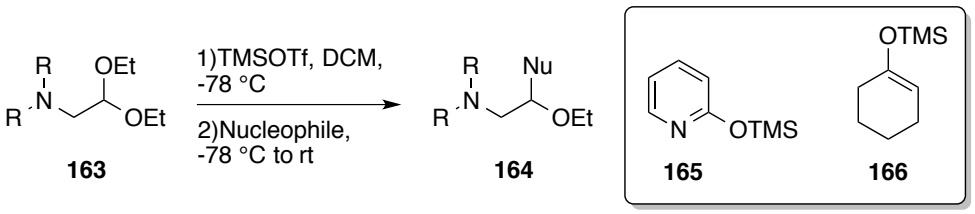
Noyori *et al*.



161 **162**

R = Cyclohexyl, Ph *etc*.

Rayner *et al*.



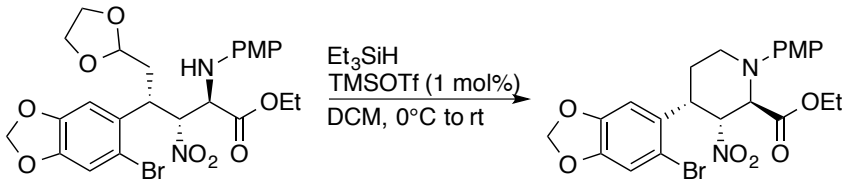
163 **164** **165** **166**

R = Allyl or Bn.

Nucleophiles = Et_2Zn, EtMgBr, **165** and **166** *etc*.

Scheme 56: Previous Lewis acid mediated acetal deprotection/reductions

Pleasingly combination of these methodologies gave the desired piperidine **100**, albeit in a yield of 22%, as one diastereomer (Scheme 57).



140 **100**
22% yield

Scheme 57: Reductive cyclisation of nitroamine **140** to piperidine **100**.

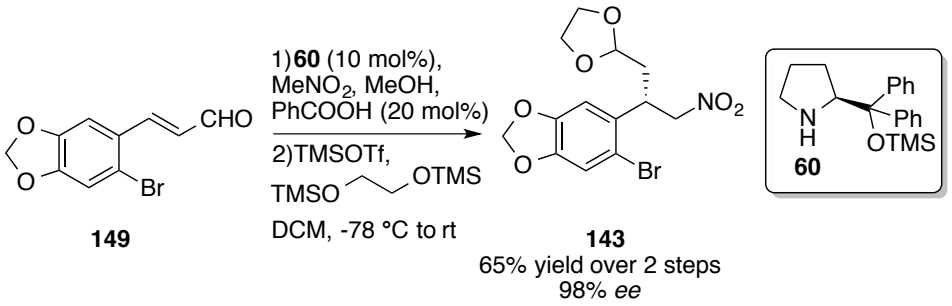
The cyclisation is assumed to proceed with retention of the relative stereochemistry and so piperidine **100** is assigned as the *trans*,*cis* diastereomer. The ^{1}H NMR spectrum is incredibly broad, so attempts to confirm the stereochemistry by inspection of the ^3J coupling constants was not possible.

4.0 Conclusions and Future Studies

4.1 Conclusions

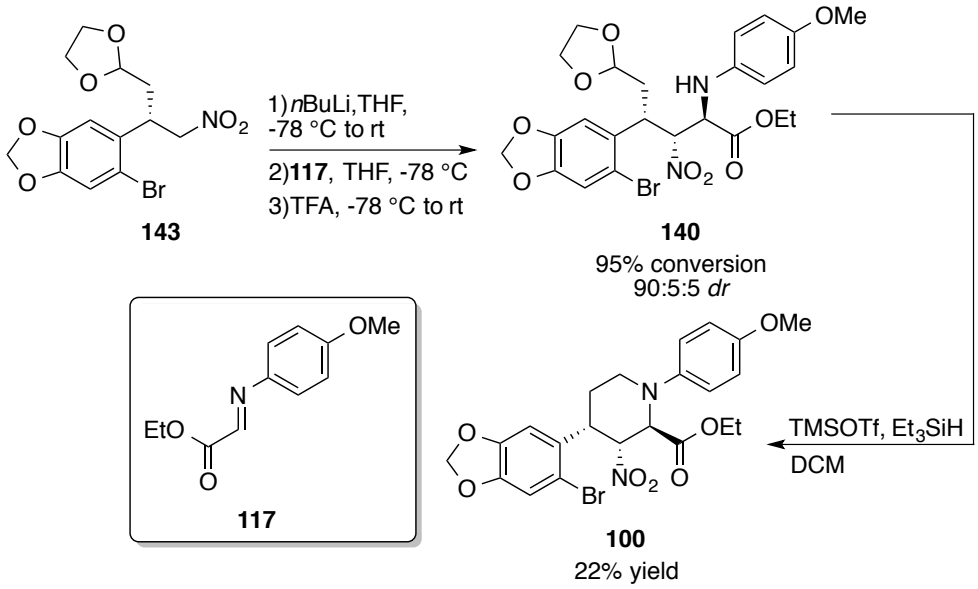
This chapter has described the work towards the first asymmetric total synthesis of Schizozygine **1**. Initial studies have shown that a three component nitro-Mannich reaction is not suitable for an asymmetric synthesis of the key nitroamine **115**. This work has highlighted that copper catalyzed addition of dialkylzincs remains an area where improvements are necessary, particularly the substrate scope of both the electrophile and nucleophile.

A revised strategy was then used, where the optically enriched nitroalkane **143** was made by an organocatalytic 1,4-addition of nitromethane to α,β-unsaturated aldehyde **149** (Scheme 58).



Scheme 58: Synthesis of optically enriched nitroalkane **143**.

This nitroalkane was then used in a nitro-Mannich reaction to give the nitroamine **140** in high diastereoselectivity. Cyclisation of nitroamine **140** was achieved by a novel one-pot deprotection/reductive amination procedure to give piperidine **100** in a yield of 22% over 2 steps, as one diastereomer (Scheme 59).



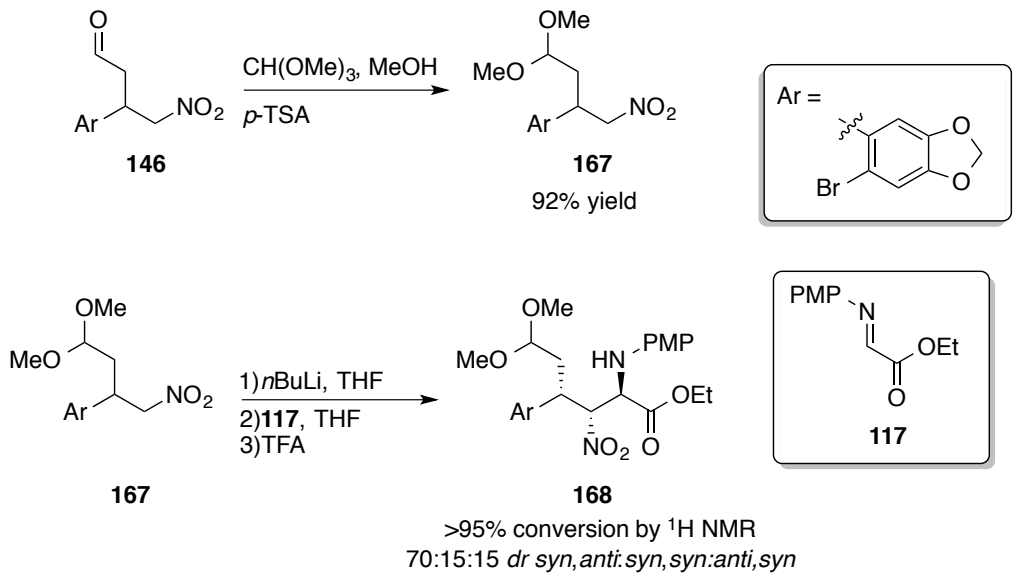
Scheme 59: Synthesis of piperidine **100**.

Other alternative nitroalkanes have also been shown as promising starting materials in this total synthesis.

4.2 Future work

4.3 Nitro-Mannich Reaction Optimisation

With the reductive cyclisation appearing to be promising, two aspects should be improved. The long time needed for deprotonation of the nitroalkane should be addressed; a possible solution is using a less hindered acetal, such as a dimethylacetal **167**. A preliminary experiment showed that dimethylacetal **167** did indeed give some positive results, when dimethylacetal **167** was treated with *n*BuLi for 45 mins and then added to imine **117** the nitro-Mannich reaction proceeded with complete conversion, but the *dr* of the nitro-Mannich step was found to be 70:15:15 (Scheme 60). The relative stereochemistry of the major diastereomer was assigned as the *syn*,*anti* diastereomer by comparison of the C*H*NO_2 signal (5.17 ppm, dd, *J* = 10.2, 4.3 Hz) as previously described.



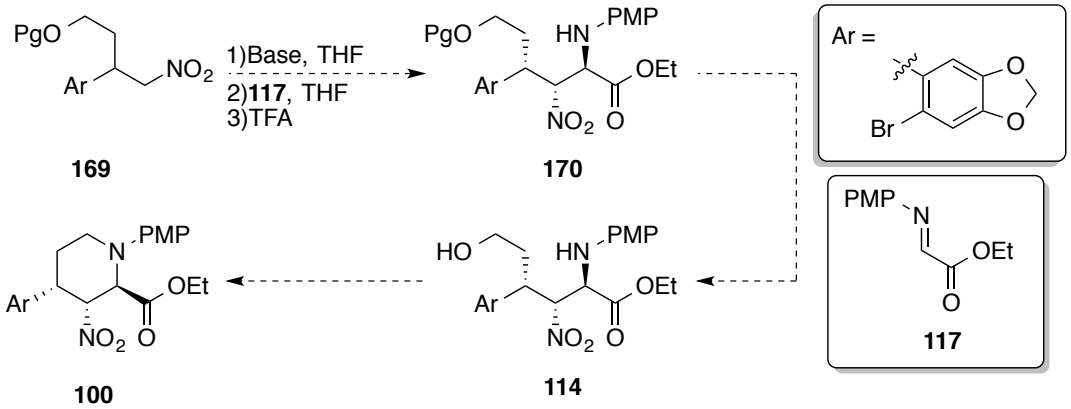
Scheme 60: Use of dimethylacetal **167** in the nitro-Mannich reaction.

The absolute stereochemistry could be controlled by using an enantioenriched sample of the dimethylacetal, this could easily be done by protection of the enantioenriched aldehyde **146** to the dimethylacetal. This result presents an opportunity to improve the synthesis of the piperidine core. As deprotonation is much quicker, it may be possible to use other bases such as LDA or LiHMDS. The more labile dimethoxy

acetal group might be more effective in the reductive cyclisation step as well.

4.4 Intramolecular Mitsunobu Strategy

Alternatively protected alcohol **169** could be used in the nitro-Mannich reaction, and the piperidine ring made by ring closure of the alcohol by a Mitsunobu reaction (Scheme 61). A strategy to make *N*-heterocycles from nitroamines using an intramolecular Mitsunobu reaction has previously been described by Anderson *et al*.[50]



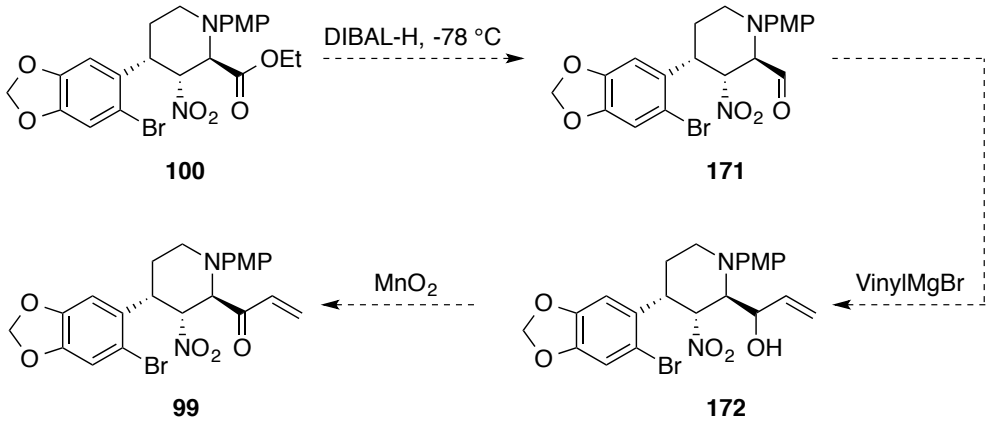
Scheme 61: Use of protected alcohol **169** in the nitro-Mannich reaction.

The enantioenriched-protected alcohol should be easily obtained from reduction of enantioenriched aldehyde **146** and then protection of the free alcohol.

4.5 Use of Different Imine Electrophiles

Currently the retrosynthesis relies on the generation of vinylketone **99** from ester **100**. This might be difficult as DIBAL-H reductions of esters frequently over reduce to the alcohol, and oxidation back to aldehyde **171** would add additional steps. In general the reaction sequence is relatively long and inefficient to just install a vinyl group (Scheme 62).

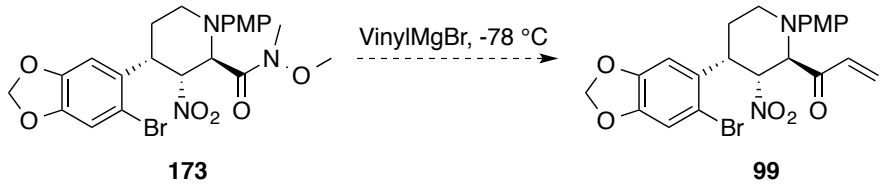
Current approach:



Scheme 62: Current strategy towards vinyl ketone **99**.

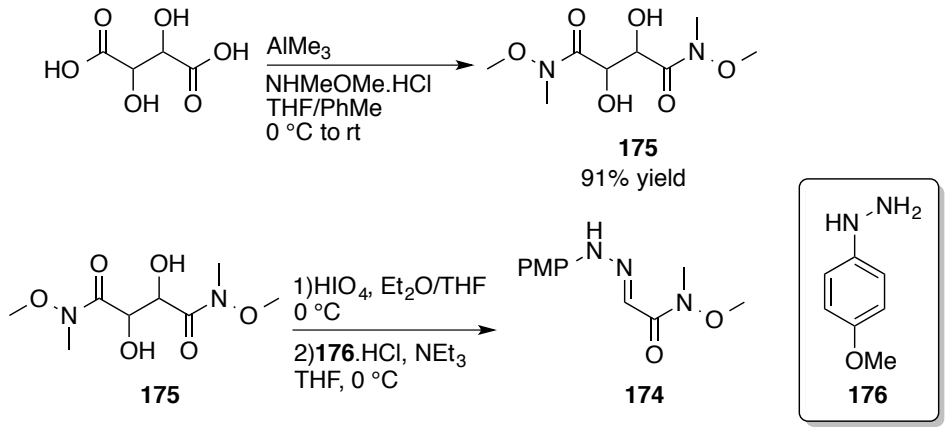
Replacement of the glyoxylate group with a Weinreb amide would reduce the number of steps and improve the atom economy (Scheme 63).

Revised approach:



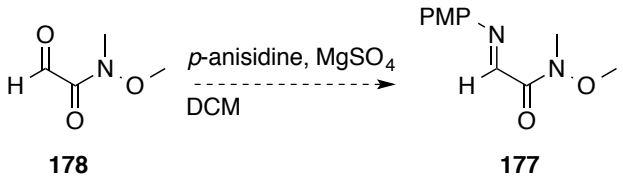
Scheme 63: Revised approach to vinyl ketone **99**.

The synthesis of a Weinreb amide aldehyde has been reported in the literature and it was used to synthesise PMP-hydrazone **174** (Scheme 64).[202]



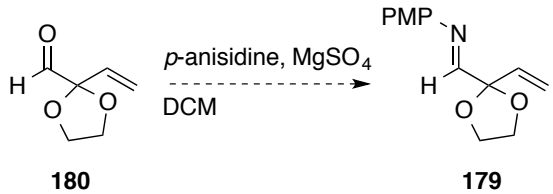
Scheme 64: Synthesis of Weinreb amide hydrazine **174**.

With such similarity to our desired *N*-PMP imine **177**, standard imine formation with *p*-anisidine should give the desired imine **177** in a high yield (Scheme 65).



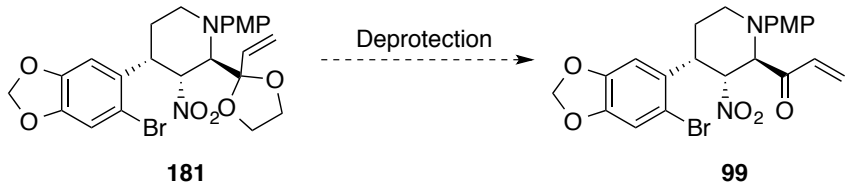
Scheme 65: Imine formation with aldehyde **178**.

Another electrophile that could be used is imine **179**, as the aldehyde **180** has been previously made by Dixon *et al*. (Scheme 66).[61]



Scheme 66: Synthesis of protected vinyl ketone-imine **179**.

The imine could then be used in the nitro-Mannich reaction. The desired vinyl ketone **99** is unmasked by simple deprotection of the acetal (Scheme 67).

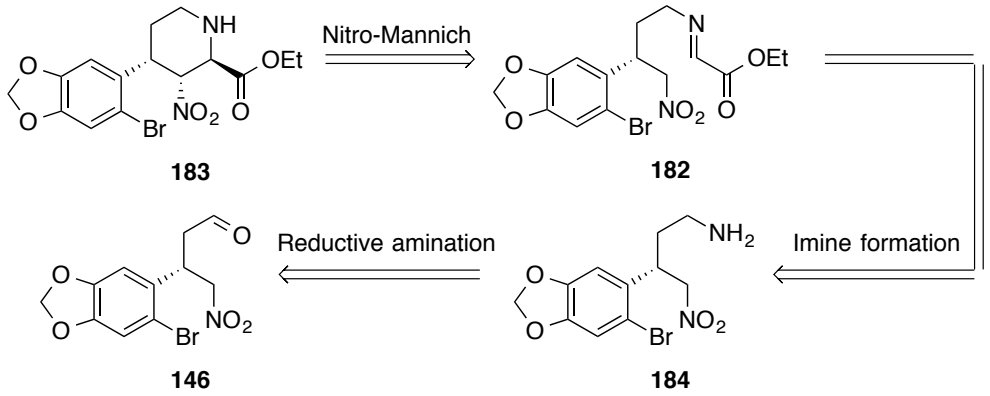


181 **99**

Scheme 67: Acetal **181** as a masked vinylketone.

4.6 Alternative Strategy to the Piperidine Ring

An intramolecular cyclisation strategy could provide an expedient approach to the piperidine core, using aldehyde **146** as a starting point (Scheme 68).[66] Previous work by Anderson *et al*. has shown that an R group on the β–position to the nitronate can control the diastereoselectivity of an intramolecular nitro-Mannich reaction, this may work on **182** too.[203] One advantage of this strategy is that the piperidine product **183** is not PMP protected, which might be useful later on in the synthesis.



Scheme 68: Intramolecular nitro-Mannich approach to the key piperidine intermediate.

5.0 Experimental

5.1 General Experimental Details

For all non-aqueous chemistry, glassware was flamed dried *in vacuo* and reactions were carried out under an inert (N_2 or Ar) atmosphere. Thin layer chromatography was performed on Polygram SilG/UV silica gel plates and visualization was performed using UV (254 nm), ninhydrin, Hannesian's stain, PMA or $KMnO_4$ solution. Flash chromatography was performed using Gedran silica gel 60, 40-63 μm. Removal of solvents *in vacuo* was achieved using the house vacuum and Büchi rotary evaporator.

5.2 Purification of Solvents and Reagents

Commercial solvents and reagents were used as supplied or purified by literature procedures. Dry solvents Et_2O, THF, DCM, toluene and hexanes were obtained from a solvents tower, where the degassed solvent ws passed through two columns of activated alumina and a 7 micron filter under 4 bar pressure. Butyl lithiums were titrated using either *N*-benzylbenzamide or diphenylacetic acid as an indicator. Ligand **131** was previously synthesised within the group and was used without further purification. Catalyst **131** was previously synthesised within the group and was used after purification (SiO_2 column, 5% MeOH/DCM).

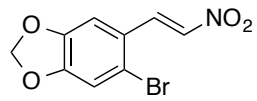
5.3 Characterisation

Melting points are reported uncorrected using a Reichert Melting Point Apparatus. All ^{1}H and ^{13}C NMR data were recorded using a Bruker ADVANCE III 40 MHz and Bruker ADVANCE III 600 MHz machines at 400 and 600 MHz for ^{1}H NMR and 100 and 125 MHz for ^{13}C. ^{19}F NMR data were recorded on a Bruker AMX 300 MHz machine at 282 MHz. All data were manipulated using ACD Labs Academic Edition or MestReNova (version 9.0). All chemical shifts (δ) are reported in parts per million (ppm), relative to residual solvent peaks δ = 7.26 for ^{1}H NMR and δ = 77.1 for ^{13}C NMR. Multiplicities for signals are denoted as s = singlet,

d = doublet, t = triplet, q = quartet, quint = quintet, p = pentet, m = multiplet and br = broad, app = apparent. Coupling constants (*J*) are reported in Hertz (Hz). ^{13}C multiplicities were assigned using DEPT. To aid assignment HMQC, HMBC and nOe were used as appropriate. Mass spectroscopy data were collected on Thermo Finnigan Mat900xp (EI/CI). Infrared data was collected using Perkin-Elmer 100 FTIR spectrometer as a thin film. Elemental analysis was performed on an Exeter Analytic Inc. EA440 horizontal load analyser. Optical rotations were obtained using a Perkin-Elmer 343 model polarimeter.

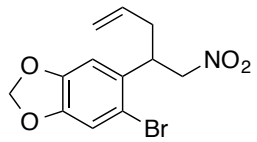
5.4 Experimental Procedures

(*E*)-5-Bromo-6-(2-nitrovinyl)benzo[*d*][1,3]dioxole **116**



A solution of 6-bromopiperonal (4.58 g, 20.0 mmol) and NH_4OAc (3.08 g, 40.0 mmol) in AcOH (80 mL) was stirred for 15 min then $MeNO_2$ (4.33 mL, 80.0 mmol) was added and the reaction mixture was heated at 117 °C for 4 h. The reaction mixture was diluted with brine (300 mL) and the product extracted with DCM (3 x 150 mL), the combined organic extracts were washed with brine (500 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude nitrostyrene **116** as a brown solid. Purification by recrystallisation (DCM/Hexanes) gave the pure nitrostyrene **116** as a yellow solid (4.35 g, 80%); mp 163-166 °C (lit.[204] 163-166 °C); R_f = 0.21 (6:4 Hexanes:DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (1H, d, *J* = 13.5 Hz, C*H*), 7.44 (1H, d, *J* = 13.5 Hz, C*H*), 7.13 (1H, s, ArH), 7.01 (1H, s, Ar*H*), 6.08 (2H, s, OCH_2O).
Data consistent with literature.[204]

5-Bromo-6-(1-nitropent-4-en-2-yl)benzo[*d*][1,3]dioxole **132**

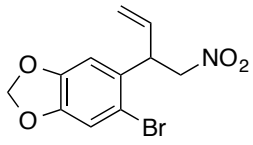


Preparation of diallylzinc: To a solution of allylmagnesium bromide (1.0 M in Et_2O, 1.00 mmol) at -78 °C was added $ZnCl_2$ (1.0 M in Et_2O, 0.50 mmol) dropwise and the reaction mixture was left to stir for 30 min. The resulting suspension was allowed to settle and the supernatant was removed by syringe and used immediately as a 0.33 M solution of diallylzinc.

To a solution of nitrostyrene **116 (**1.28 g, 5.00 mmol) and $Cu(OTf)_2$ (18 mg, 0.05 mmol, 1 mol%) in Et_2O (10 mL) was added diallylzinc (32.3 mL, 5.50 mmol, 0.17 M in Et_2O) dropwise at -78 °C and left to stir for 10 minutes and then brought to room temperature and stirred for 1 hour. The

reaction mixture was diluted with brine (100 mL), the product was extracted with EtOAc (3 x 50 mL) and then the combined organic layers dried (Na_2SO_4), and concentrated *in vacuo* to give the crude nitroalkane **132.** Purification by column chromatography (7:3 Hexanes:DCM) gave the pure nitroalkane **132** as a yellow oil (1.54 g, 98%); R_f = 0.60 (7:3 pet. Ether:EtOAc); IR ν_{max} (neat) 2906 (=CH_2), 1548 (N-O), 1376 (N-O), 1233 (C-O) cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.03 (1H, s, Ar*H*), 6.66 (1H, s, Ar*H*), 5.99 (1H, d, *J* = 1.4 Hz, OC*H*HO), 5.98 (1H, d, *J* = 1.4 Hz, OCH*H*O), 5.68 (1H, ddt, *J* = 17.1, 10.2, 7.0 Hz, C*H*), 5.10 (1H, dd, *J* = 17.1, 1.6 Hz, CHC*H*H), 5.08 (1H, dd, *J* = 10.0, 1.2 Hz, CHCH*H*), 4.56 (2H, d, *J* = 7.3 Hz, CH_2NO_2), 4.10 (1H, app. p, *J* = 7.3 Hz, ArC*H*), 2.45 (2H, td, *J* = 7.3, 1.7 Hz, CHCH_2); ^{13}C NMR ($CDCl_3$, 151 MHz) 148.0 (Ar*C*), 147.8 (Ar*C*), 133.8 (*C*HCH$_2$), 131.0 (ArC), 118.7 (CH*C*H$_2$), 115.4 (Ar*C*), 113.4 (Ar*C*H), 107.4 (Ar*C*H), 102.1 (O*C*H$_2$O), 78.6 (*C*H$_2$NO$_2$), 42.1 (ArCC*H*), 36.8 (CHCH$_2$); m/z (EI) 226 (100%, M^+-$C_3H_3NO_2$); HRMS $C_{12}H_{12}(^{79}Br)NO_4$ calcd. 312.9945, found 312.9945.

5-Bromo-6-(1-nitrobut-3-en-2-yl)benzo[*d*][1,3]dioxole **133**

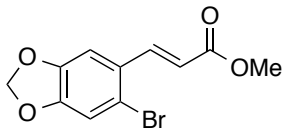


Preparation of divinylzinc: To a solution of vinylmagnesium bromide (1.0 M in Et_2O, 1.00 mmol) -78 °C was added $ZnCl_2$ (1.0 M in Et_2O, 0.50 mmol) dropwise at left to stir for 30 min. The resulting suspension was allowed to settle and the supernatant was removed by syringe and used immediately as a 0.33 M solution of divinylzinc.

To a solution of nitrostyrene **116** (54 mg, 0.20 mmol) and $Cu(OTf)_2$ (3.62 mg, 0.01 mmol, 5 mol%) in PhMe (2 mL) was added divinylzinc (667 µL, 0.22 mmol, 0.33 M in Et_2O) dropwise at -78 °C and left to stir for 2 h. The reaction mixture was added sat. $NaHCO_3$ (50 mL), the product was extracted with EtOAc (3 x 30 mL), the combined organic extracts were

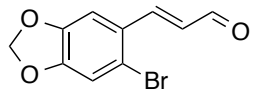
washed with brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give the crude nitroalkane **133** as a yellow wax. Purification by column chromatography (9:1 Hexanes:DCM) gave the pure nitroalkane **133** as a yellow oil (49 mg, 82%); R_f = 0.25 (9:1 pet.Ether:EtOAc); IR ν_{max} (neat) 2911 (=CH_2), 1553 (N-O), 1377 (N-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.05 (1H, s, ArC*H*), 6.71 (1H, s, ArC*H*), 6.00 – 5.98 (2H, m, OCH_2O), 5.93 (1H, ddd, *J* = 17.2, 10.4, 6.8 Hz, CH*H*), 5.31 – 5.19 (2H, m, C*H* & C*H*H), 4.73 – 4.67 (1H, m, C*H*), 4.64 – 4.57 (2H, m, CH_2NO_2); ^{13}C NMR (151 MHz, $CDCl_3$) δ 148.0 (2x Ar*C*), 134.5 (Ar*C*), 130.0 (Ar*C*), 118.6 (*C*H_2), 115.0 (Ar*C*H), 113.5 (Ar*C*H), 108.2 (*C*H), 102.2 (O*C*H_2O), 77.9 (*C*HNO_2), 46.1 (*C*H); m/z (EI) 299 (68%, [$M^{+\cdot}$]); HRMS $C_{11}H_{10}(^{79}Br)NO_4$ calcd. 298.9788, found 298.9787.

Methyl (*E*)-3-(6-bromobenzo[*d*][1,3]dioxol-5-yl)acrylate **156**



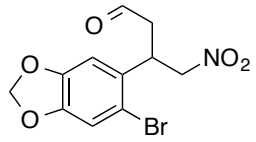
A solution of trimethylphosphonoacetate (3.02 mL, 18.7 mmol) in THF (100 mL) was cooled to 0 °C. To the reaction mixture was added KO*t*Bu (2.09 g, 18.7 mmol) and the reaction mixture was left to stir for 1 h, a solution of 6-bromopiperonal (4.28 g, 18.7 mmol) in THF (50 mL) was added dropwise and the solution was then left to stir for 18 hours at rt. The reaction mixture was added sat. NH_4Cl (100 mL), the product was extracted with DCM (3 x 100 mL), the combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give the crude ester **156** as an off-white solid. Purification by recrystalisation (EtOAc) gave the pure ester **156** as a white Solid (4.82 g, 96%); mp 158-160 °C (lit.[205] 162-164 °C); R_f = 0.30 (9:1 pet. Ether:EtOAc) 1H NMR ($CDCl_3$) 7.99 (1H, d, *J* = 15.9 Hz, C*H*), 7.06 (1H, s, Ar*H*), 7.06 (1H, s, Ar*H*), 6.24 (1H, d, *J* = 15.9 Hz, C*H*), 6.02 (2H, s, OCH_2O), 3.81 (3H, s, OCH_3).
Data consistent with literature.[205]

(*E*)-3-(6-Bromobenzo[*d*][1,3]dioxol-5-yl)acrylaldehyde **149**



To a solution of ester **156** (4.06 g, 14.2 mmol) in DCM (43 mL) at 0 °C was added DIBAL-H (25.1 mL, 42.6 mmol, 1.7M in PhMe) and then stirred for 2 h at rt. To the reaction mixture was added sat. Rochelle's salt solution (200 mL), the product was extracted with DCM (3 x 100 mL), the combined organic extracts dried (Na_2SO_4) and concentrated *in vacuo* to give crude alcohol as an off-colour solid. The crude alcohol was dissolved in DCM (50 mL) and MnO_2 (8.70 g, 100 mmol) was added and the reaction mixture was left to stir for 24 h. The reaction mixture was filtered through a pad of Celite (EtOAc and DCM wash) and concentrated *in vacuo* to give the crude aldehyde **149** as a yellow solid. Purification by recrystallisation (EtOAc) gave the pure aldehyde **149** as an off-white solid (3.26 g, 90%); mp 141-143 °C; R_f = 0.43 (7:3 pet. Ether:EtOAc); IR ν_{max} (neat) 1666 (C=O), 1610 (C=C), 1244 (C-O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 9.72 (1H, d, *J* = 7.7 Hz, C*H*O), 7.82 (1H, d, *J* = 15.8 Hz, C*H*), 7.10 (2H, s, Ar*H*), 6.52 (1H, dd, *J* = 15.8, 7.7 Hz, C*H*), 6.06 (2H, s, OCH_2O); ^{13}C NMR ($CDCl_3$, 151 MHz) 193.7 (*C*HO), 151.0 (Ar*C*), 150.7 (*C*H), 148.3 (Ar*C*), 129.0 (*C*H), 127.2 (Ar*C*), 118.9 (Ar*C*), 113.5 (Ar*C*H), 106.7 (Ar*C*H), 102.6 (O*C*H_2O); m/z (ESI) 226 (100%, M+H^+); HRMS $C_{10}H_8(^{79}Br)O_3$ calcd. 254.9664, found 254.9657; Anal. cald. for $C_{10}H_7BrO_3$: C, 47.09; H, 2.77; found: C, 46.89; H, 2.74%.

3-(6-Bromobenzo[*d*][1,3]dioxol-5-yl)-4-nitrobutanal **146**

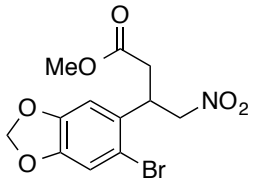


Enantioenriched sample: To a suspension of aldehyde **149** (638 mg, 2.50 mmol) and PhCOOH (61 mg, 0.50 mmol, 20 mol%) in MeOH (5 mL) was added (*R*)-TMS-Prolinol **60** (82 mg, 0.25 mmol, 10 mol%) and then $MeNO_2$ (401 µL, 7.50 mmol) and left to stir for 24 hours. The reaction mixture was added sat. $NaHCO_3$ (100 mL), the product was extracted with EtOAc (3 x 50 mL), the combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give the crude aldehyde **146** as a bright red wax. Purification by column chromatography (7:3 Hexanes:EtOAc) gave the pure aldehyde **146** as an orange oil (593 mg, 75%); R_f = 0.13 (8:2 pet.Ether:EtOAc); $[\alpha]_D^{20}$= 62.2 (c = 0.55, acetone); IR ν_{max} (neat) 1709 (C=O), 1546 (N-O), 1375 (N-O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.71 (1H, d, *J* = 1.1 Hz, C*H*O), 7.03 (1H, s, Ar*H*), 6.67 (1H, s, Ar*H*), 5.99 – 5.96 (2H, m, OCH_2O), 4.71 – 4.62 (m, 2H, CH_2NO_2), 4.48 (1H, app. p, *J* = 6.9 Hz, C*H*), 3.01 (1H, dd, *J* = 18.2, 7.1 Hz, C*H*H), 2.93 (1H, dd, *J* = 18.2, 7.0 Hz, CH*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.7 (*C*HO), 148.2 (2x Ar*C*), 129.9 (2x Ar*C*), 113.6 (2x Ar*C*H), 102.3 (O*C*H_2O), 77.8 (*C*HNO_2), 45.6 (*C*H_2), 37.0 (*C*H); m/z (EI) 315 (100%, [M-H^+]); HRMS $C_{11}H_{10}(^{79}Br)NO_5$ calcd. 314.9737, found 314.9740; Anal. calcd. for $C_{11}H_{10}BrNO_5$: C, 41.80; H, 3.19; N, 4.43; found: C, 41.83; H, 3.16; N, 4.39.

Racemic Sample: To a solution of allyl nitroalkane **132** (314 mg, 1.00 mmol) in dioxane/H_2O (3:1, 10 mL) was added OsO_4 (5 mg, 0.02 mmol, 2 mol%) and 2,6-lutidine (232 µL, 2.00 mmol) and then left to stir for 5 min. The reaction mixture was added $NaIO_4$ (1.71 g, 8.00 mmol) and stirred for 3 h. The reaction mixture was added brine (30 mL), the product was extracted with EtOAc (3 x 20 mL), the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give the crude aldehyde **146** as a brown oil. Purification by column chromatography (6:4 to 1:1

Hexanes:EtOAc) gave the pure aldehyde **146** as a colourless oil (225 mg, 71 %); ^{1}H NMR data the same as above.

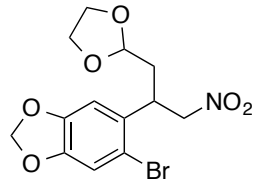
Methyl 3-(6-bromobenzo[*d*][1,3]dioxol-5-yl)-4-nitrobutanoate **148**



Enantioenriched sample: To a solution of aldehyde **146** (79 mg, 0.25 mmol) in *t*BuOH (2 mL) was added 2-methyl-2-butene (1.37 mL, 12.9 mmol), H_2O (500 µL), $NaClO_2$ (117 mg 1.29 mmol) followed by NaH_2PO_4 (161 mg, 1.03 mmol) and then left to stir for 1 h. The reaction mixture was diluted with brine (30 mL), the product was extracted with DCM (3 x 15 mL), the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* give the crude carboxylic acid as a colourless oil. The residue was dissolved in 9:1 DCM:MeOH (2 mL) and added $TMSCHN_2$ (260 µL, 0.52 mmol, 2 M in Et_2O) and then stirred for 30 min. The reaction mixture was added AcOH (20 µL, 0.39 mmol) and concentrated *in vacuo* to give the crude ester **148** as an orange gum. Purification by column chromatography (8:2 to 7:3 Hexanes:EtOAc) gave the pure ester **148** as a colourless oil (80 mg, 96%); R_f = 0.33 (8:2 pet.Ether:EtOAc); $[\alpha]_D^{20}$= 60.0 (c = 0.01, $CHCl_3$); IR ν_{max} (neat) 1731 (C=O), 1551 (N-O), 1335 (N-O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04 (1H, s, Ar*H*), 6.68 (1H, s, Ar*H*), 5.99 (1H, d, *J* = 1.4 Hz, OC*H*HO), 5.98 (1H, d, *J* = 1.4 Hz, OC*H*HO), 4.71 (2H, d, *J* = 6.9 Hz, CH_2NO$_2$), 4.40 (1H, app. p, *J* = 7.0 Hz, C*H*), 3.67 (3H, s, OCH_3), 2.92 – 2.66 (2H, m, CH_2); ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.1 (*C*O), 148.1 (2x Ar*C*), 130.0 (2x Ar*C*), 113.6 (2x *C*H), 102.2 (O*C*H$_2$O), 77.9 (CH$_2$NO$_2$), 52.2 (O*C*H$_3$), 38.9 (*C*H), 36.3 (*C*H$_2$); m/z (CI) 365 (100%+, [M+NH$_4^+$]); HRMS $C_{12}H_{13}(^{79}Br)NO_6$ calcd. 344.9843, found 344.9842; HPLC analysis (Chiralcel OD, hexane/*iso*-propranol 9:1, flow rate = 1 mL/min, λ = 254 nm): retention time t_r (major) = 21.7 min, t_r (minor) = 37.9 min, shows 97% ee.

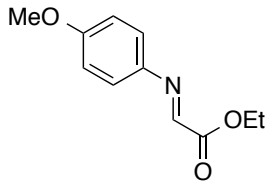
Racemic sample: To a solution of ester **156** (2.00 g, 7.00 mmol) in MeCN (20.0 mL) was added $MeNO_2$ (5 mL) and DBU (522 µL, 7.00 mmol) and left to stir for 10 h. The reaction mixture was added brine (100 mL), the product was extracted with DCM (3 x 75 mL), the combined organic extracts dried (Na_2SO_4) and concentrated *in vacuo* to give the crude ester **148** as a golden oil. Purification by column chromatography (8:2 to 7:3 pet.Ether:EtOAc) gave the pure ester **148** as a colourless oil (1.76 g, 73%); data the same as above.

5-(1-(1,3-Dioxolan-2-yl)-3-nitropropan-2-yl)-6-bromobenzo[*d*][1,3]dioxole **140**



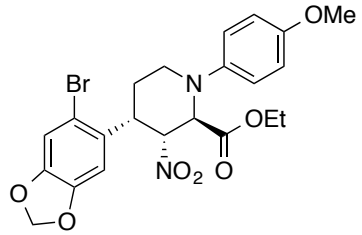
To a solution of **146** (237 mg, 0.75 mmol) in DCM (1.00 mL) was added TMSOTf (14.0 µL, 0.075 mmol) and then 1,2-disiloxyethane (183 µL, 0.75 mmol) at -78 °C. The reaction mixture was brought to rt and stirred for 18 h. The reaction mixture was concentrated *in vacuo* to give the crude acetal **140** as a brown oil. Purification by column chromatography (7:3 Hexanes:EtOAc) gave the pure acetal **140** as a colourless oil (237 mg, 87%); R_f = 0.36 (7:3 Hexanes:EtOAc); $[\alpha]_D^{20}$= -63.6 (c = 0.33, acetone); IR ν_{max} (neat) 1545 (N-O), 1380 (N-O), 1123 (C-O) cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.02 (1H, s, Ar*H*), 6.71 (1H, s, Ar*H*), 5.98 (1H, d, *J* = 1.4 Hz, OC*H*HO), 5.97 (1H, d, *J* = 1.4 Hz, OCH*H*O), 4.82 (1H, dd, *J* = 5.6, 3.5 Hz, C*H*CH_2NO_2), 4.69 – 4.62 (1H, m, CH*H*NO_2), 4.67 – 4.63 (1H, m, C*H*HNO_2), 4.24 (1H, s, C*H*), 3.94 – 4.00 (2H, m, OCH_2CH_2O), 3.79 – 3.88 (2H, m, OCH_2CH_2O), 2.06 – 2.13 (1H, m, CH*H*), 2.02 (1H, ddd, *J* = 14.4, 7.1, 5.7 Hz, C*H*H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 148.0 (2x Ar*C*), 147.8 (Ar*C*), 131.3 (Ar*C*), 113.5 (2x *C*H), 102.4 (O*C*HO), 102.1 (OCH_2O), 79.0 (CH_2NO_2), 65.2 (CH_2O), 65.0 (CH_2O), 38.6 ($CHCH_2NO_2$), 36.4 (CH_2); m/z (EI) 72 (100%, $C_3H_5O_2^{\cdot}$), 280 (10%, M-Br^+); HRMS $C_{13}H_{14}(^{79}Br)NO_6$ calcd. 358.9999, found 359.0006; Anal. calcd. for $C_{11}H_9BrO_5$: C, 43.35; H, 3.92; N, 3.85; found: C, 43.31; H, 3.89; N, 3.85; HPLC analysis (Chiralcel OD, hexane/*iso*-propranol 9:1, flow rate = 1 mL/min, λ = 254 nm): Retention time t_r (minor) = 33.6 min, t_r (major) = 42.6 min, shows 98% *ee*.

Ethyl (*E*)-2-((4-methoxyphenyl)imino)acetate **117**



To a solution of *p*-anisidine (5.00 g, 40.6 mmol) in DCM (40 mL) was added Na_2SO_4 (20.0 g) then ethyl glyoxylate (50% w/w in PhMe, 8.20 mL, 40.6 mmol) and left to stir for 18 h. The reaction mixture was filtered and concentrated *in vacuo* to give the crude imine **117** as a green/brown oil (7.56 g, 90%), which was used without further purification; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.94 (1H, s, C*H*N), 7.37 (2H, d, *J* = 8.9 Hz, Ar*H*), 6.94 (1H, d, *J* = 9.0 Hz, Ar*H*), 4.42 (2H, q, *J* = 7.1 Hz, OCH_2), 3.84 (3H, s, ArOCH_3), 1.41 (3H, t, *J* = 7.1 Hz, CH_2CH_3).
Data consistent with literature.[206]

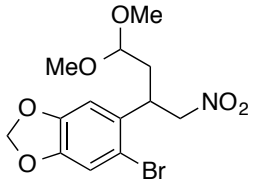
Ethyl (2*R**,3*R**,4*S**)-4-(6-bromobenzo[*d*][1,3]dioxol-5-yl)-1-(4-methoxyphenyl)-3-nitropiperidine-2-carboxylate **100**



To a solution of crude nitroamine **140** (113 mg, 0.20 mmol) in DCM (1 mL) was added TMSOTf (0.36 µL, 2.00 µmol, 1 mol%), followed by Et_3SiH (32 µL, 0.20 mmol) at 0 °C and then stirred for 6 h at rt. The reaction mixture was added $NaHCO_3$ (40 mL), the product was extracted with EtOAc (3 x 20 mL), the combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give the crude piperidine **100** as a brown gum. Purification by column chromatography (9:1 DCM:Hexanes) gave the pure piperidine **100** as a brown gum (22 mg, 22%); R_f = 0.30 (9:1 DCM:Hexanes); IR ν_{max} (neat)

1739 (C=O), 1553 (N-O), 1373 (N-O), 1216 (C-O), 1036 (C-N) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.12 (2H, d, *J* = 8.4 Hz, Ar*H*), 7.00 (1H, s, Ar*H*), 6.88 – 6.82 (3H, m, Ar*H*), 6.01 - 5.96 (2H, m, OCH_2O), 5.17 (1H, s, C*H*Ar), 4.28 (1H, d, *J* = 8.8 Hz, C*H*NO_2), 4.04 – 3.94 (3H, m, CH_2CH_3 & C*H*), 3.78 (3H, s, OCH_3), 3.33 (1H, d, *J* = 12.2 Hz, C*H*H), 3.10 – 2.99 (1H, m, C*H*H), 2.09 – 1.85 (1H, m, CH_2), 1.01 (3H, t, *J* = 7.1 Hz, CH_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.8 (*C*O), 157.1 (Ar*C*), 148.2 (Ar*C*), 147.9 (Ar*C*), 143.0 (Ar*C*), 131.0 (Ar*C*), 124.5 (2x Ar*C*H), 114.5 (Ar*C*H), 113.4 (Ar*C*H), 113.4 (O*C*H_2O), 102.2 (Ar*C*), 89.4 (*C*HNO_2), 67.7 (*C*HAr), 62.0 (*OC*H_2CH_3), 55.6 (*C*H_3), 54.9 (*C*H_2), 44.4 (*C*HCO_2Et), 31.3 (*C*H_2) 13.9 (*C*H_3); m/z (ESI+) 507 (100%, [M+H^+]); HRMS $C_{22}H_{24}(^{79}Br)N_2O_7$ calcd. 507.0820, found 507.0797.

5-Bromo-6-(4,4-dimethoxy-1-nitrobutan-2-yl)benzo[*d*][1,3]dioxole **167**



To a solution of aldehyde **146** (494 mg, 1.36 mmol) in MeOH (5.5 mL) was added trimethyl orthoformate (447 µL, 4.08 mmol) and *p*-TSA (12 mg, 0.07 mmol) and heated at reflux for 3 h. The reaction mixture was added sat. K_2CO_3 (100 mL), the product was extracted with DCM (3 x 75 mL), the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give the crude acetal **167** as a yellow oil. Purification by column chromatography (7:3 Hexanes:EtOAc) gave the pure acetal **167** as a colourless oil (466 mg, 95%); R_f = 0.31 (7:3 Hexanes:EtOAc); IR ν_{max} (neat) 1549 (N-O), 1376 (N-O), 1120 (C-O) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03 (1H, s, Ar*H*), 6.69 (1H, s, Ar*H*), 5.99 (1H, d, *J* = 1.3 Hz, OC*H*HO), 5.98 (1H, d, *J* = 1.3 Hz, OCH*H*O), 4.65 – 4.52 (2H, m, CH_2NO_2), 4.23 (1H, dd, *J* = 7.1, 4.0 Hz, C*H*), 4.20 – 4.13 (1H, m, C*H*), 3.32 (3H, s, OCH_3), 3.27 (3H, s, OCH_3), 2.06 – 1.92 (2H, m, CH_2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.1 (Ar*C*), 147.9 (Ar*C*), 131.2 (2 x Ar*C*), 113.5 (2 x Ar*C*H), 102.4 (*C*H), 102.2 (O*C*H_2O), 79.1 (*C*H_2NO_2), 53.8

(OCH_3), 53.0 (OCH_3), 38.9 (*C*H), 35.6 (CH_2); m/z (EI) 361 (10%, $M^{+\cdot}$); HRMS $C_{13}H_{16}(^{79}Br)NO_4$ calcd. 361.0156, found 361.0157.

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